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(54) Use of cyclooxygenase-2 inhibitors for the treatment and prevention of tumors, tumor-related disorders and cachexia

(57) Certain cyclooxygenase-2 inhibitors are useful for the treatment and prevention of tumours and tumour-related disorders and cachexia.

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Description

[0001] The present invention relates to the use of certain compounds, specifically cyclooxygenase-2 inhibitors (hereinafter referred to as "COX-2 inhibitors") for the treatment and prevention of tumours and tumour-related disorders and cachexia.

[0002] Cachexia is a systemic disease of which the cardinal symptoms are progressive weight loss, anemia, edema, loss of appetite and so forth. It may occur as a side-effect of certain chronic diseases, such as malignant tumours, tuberculosis, diabetes, blood diseases, endocrine diseases, infections and acquired immune deficiency syndrome. When cachexia occurs as a result of the presence of a malignant tumour, even if the administration of anti-tumour drugs to the patient with a malignant tumour is effective and anti-tumour effects are experienced, there is normally no improvement in the cachexia because of adverse effects such as the myelotoxicity which may be caused by the anti-tumour drug.

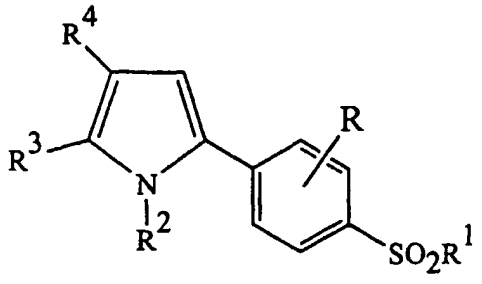
[0003] The treatment of cachexia is often very difficult for the following reasons:

[0004] Since the strength of a patient is greatly depleted as cachexia progresses, it may become impossible to continue treatment using anti-tumour drugs (which generally exhibit a high level of toxicity), and this thereby becomes an obstacle to the treatment of the malignant tumour.

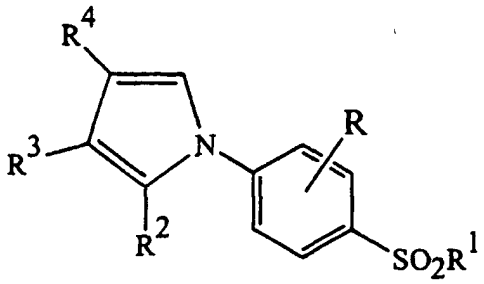
[0005] Nutritional supplements are often given in order to treat the symptoms of cachexia. This, however, often enhances the progress of the malignant tumour, and may shorten the survival time of the patient.

[0006] At present, no satisfactory treatment for cachexia has been established, and there is an increasing need for agents that alleviate the symptoms of cachexia.

[0007] The compounds of formula (I) or (II), shown below, which, with certain other compounds, are the active ingredients of the compositions of the present invention, are known to inhibit selectively cyclooxygenase-2 (COX-2). They are also known to inhibit the production of inflammatory cytokines (particularly IL-1 and TNF-α), to inhibit the production of leukotrienes (particularly LTB_4), to inhibit bone resorption, and to have analgesic, anti-inflammatory and anti-pyretic effects (European Patent Publication No. 799 823A).



(I)



(II)

[0008] It has not previously been known that these compounds can be used for the treatment or prevention of cachexia.

[0009] Also, although it is known that certain other active ingredients employed in the present invention, namely the compounds of formula (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI), (XII), (XIII) and (XIV) have selective inhibitory activity against cyclooxygenase-2, an inhibitory effect on the production of inflammatory cytokines (particularly IL-1 and TNF-α), an inhibitory action on the production of leukotrienes (particularly LTB_4), an inhibitory action on bone resorption, an analgesic action, an anti-inflammatory action and an antipyretic action [International publication number WO95/00501, J. Med. Chem., 40, 1347 (1997), International publication number WO94/13635, Pharmacology, 55, 44 (1997), Prostaglandins, 47, 55 (1994), Japanese publication number Hei 9-52882, Jpn. J. Pharmacol., 67,305 (1995), Inflamm. Res., 47, Suppl. 3, S257 (1997), J. Med. Chem., 38, 4570 (1995), US Patent No. 5 474 995, European Patent No. 863 134 and International Patent Publication No. WO 98/06708], it has not previously been disclosed that these compounds have an effect against cachexia.

[0010] It is known from epidemiological studies that the taking of conventional NSAIDS (non-steroidal anti-inflammatory drugs, which are COX-1 and COX-2 inhibitors), the most common of which is aspirin, and the incidence of colon cancer have an inverse correlation. In addition, there have been many reports that NSAIDS, such as aspirin and sulindac, have shown inhibitory activity against tumour metastasis and carcinogenesis in preclinical studies. Some

NSAIDS have been used in clinical studies for the prevention of colon carcinogenesis.

[0011] However, since conventional NSAIDS are not selective for COX-1 or COX-2, the occurrence of adverse effects is unavoidable.

[0012] It would, therefore, be desirable to discover a selective cyclooxygenase-2 inhibitor (selective COX-2 inhibitor) for use as an anti-tumour agent that has a low level of adverse effects.

[0013] Among the known selective COX-2 inhibitors, it is known that MF-tricyclic [Oshima, M. *et al.* "Suppression of Intestinal Polyposis in APCΔ^{716} Knockout Mice by Inhibition of Cyclooxygenase 2 (COX-2)", Cell, 87, 803-809 (1996)] and celecoxib (Reddy, R.S. *et al.* "Evaluation of Cyclooxygenase-2 Inhibitor for Potential Chemopreventive Properties in Colon Carcinogenesis", Cancer Res., 56, 4566-4569 (1996)] inhibit the occurrence of experimental colonic polyposis, and that SC-58125 exhibits growth inhibitory effects against certain types of human colon cancer cell lines (Sheng, H. *et al.* "Inhibition of Human Colon Cancer Cell Growth by Selective Inhibition of Cyclooxygenase-2", J. Clin. Invest., 99, 2254-2259 (1997)].

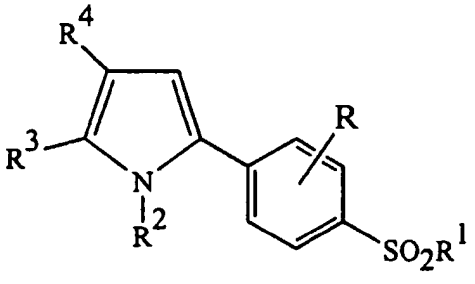
[0014] However, in the case of the former, the experimental system used is not a model for an established colon cancer, and the compounds are only able to prevent the occurrence of polyposis in the preliminary stage of colon cancer.

[0015] On the other hand, with respect to the latter, the only colon cancer cell line in which growth inhibitory effects against human colon cancer cell lines have been observed is a cell line that expresses cyclooxygenase-2 (human colon cancer cell line HCA-7), and it has been disclosed that colon cancer cell lines that do not exhibit tumour growth inhibitory activity (HCT-116) *in vitro* do not exhibit tumour growth inhibitory effects *in vivo*. Thus, whether or not COX-2 inhibitor-induced tumour growth inhibitory effects on colon cancer are expressed *in vivo* depends on the sensitivity of the colon cancer cell lines used against COX-2 inhibitor-induced cell growth inhibitory activity *in vitro*. It is thus unlikely that the tumour growth inhibitory effects of COX-2 inhibitors *in vivo* would be observed against various other cancers, especially those cancers, including colon cancers, that are resistant to COX-2 inhibitor-induced inhibition of cell growth *in vitro* and that do not express cyclooxygenase-2.

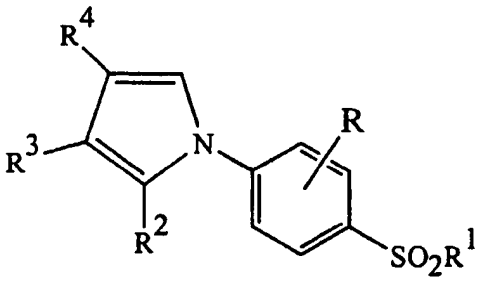
[0016] Moreover, there has been no previous disclosure of the use of a combination of a selective cyclooxygenase-2 inhibitor and a 5-fluorouracil derivative for the prevention or inhibition of tumour growth.

[0017] We have now found that certain 1,2-diphenylpyrrole derivatives and closely related compounds have excellent activity for the prevention or inhibition of cachexia, and that these 1,2-diphenylpyrrole derivatives are effective for the treatment or prevention of tumour-related disorders, alone or in combination with a 5-fluorouracil derivative.

[0018] Thus, in a first embodiment, the present invention provides the use of a compound of formula (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI), (XII), (XIII) or (XIV) for the manufacture of a medicament for the treatment or prevention of cachexia. The compounds may be used to treat cachexia in a mammal, which may be human, in need of such treatment or prevention. The compounds of the present invention are compounds of formula (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI), (XII), (XIII) or (XIV):



(I)



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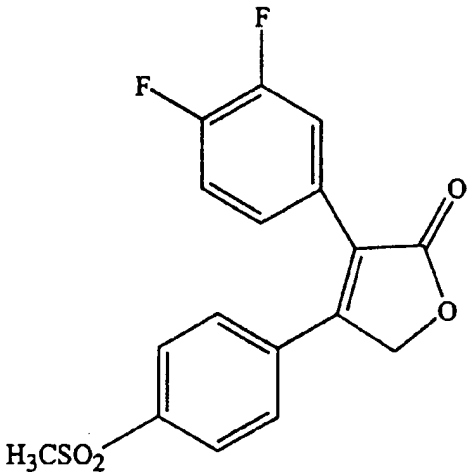

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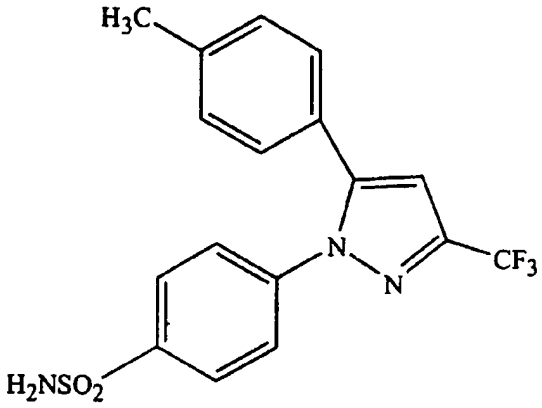

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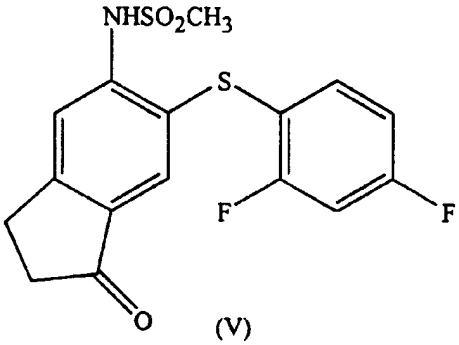

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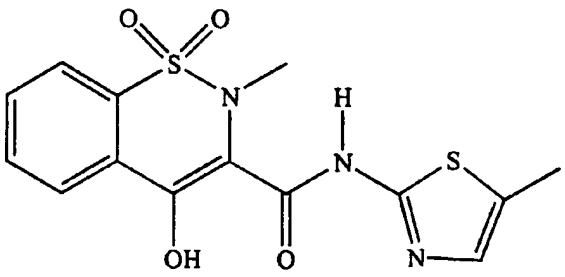

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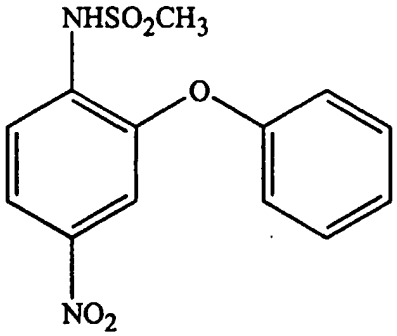

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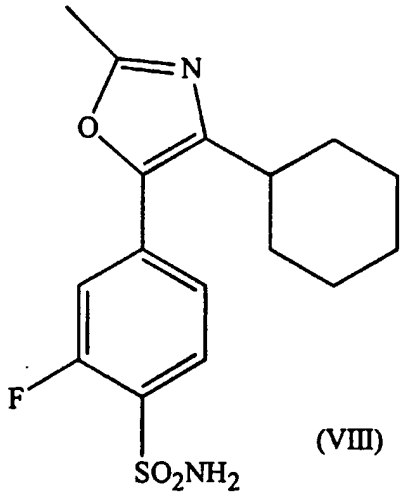

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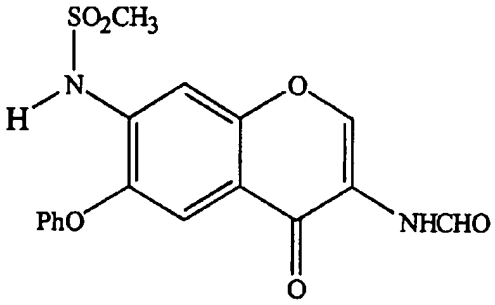

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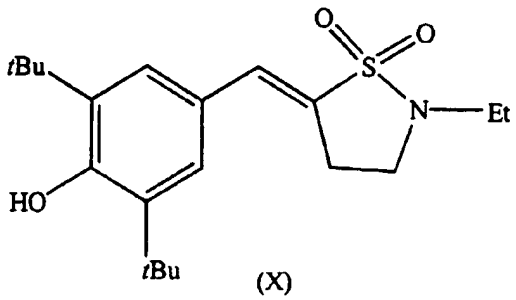

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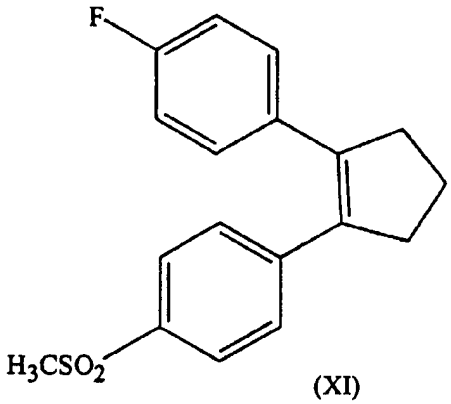

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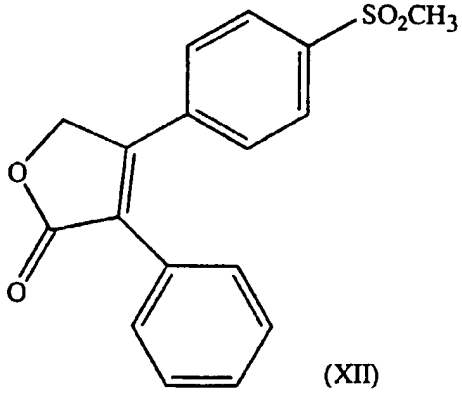

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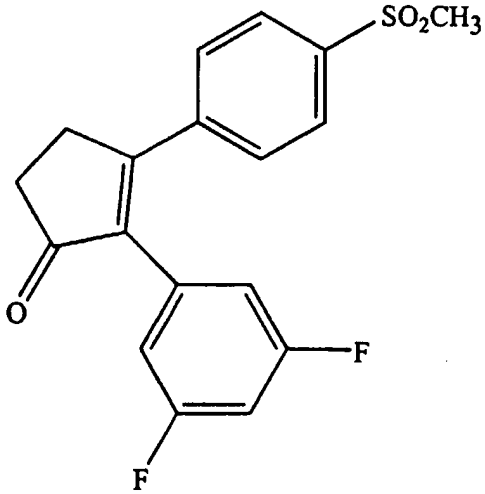

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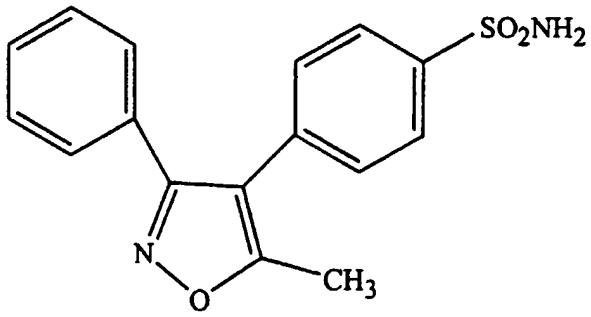


(XIV)

in which

R represents a hydrogen atom, a halogen atom or a lower alkyl group;

R^1 represents a lower alkyl group, an amino group or a group of formula -NHR^a (in which R^a represents a group which may be eliminated *in vivo);*

R^2 represents a phenyl group or a phenyl group which is substituted by at least one of substituents α or substituents β, defined below;

R^3 represents a hydrogen atom, a halogen atom, a lower alkyl group or a lower alkyl group which is substituted by at least one of substituents α;

R^4 represents a hydrogen atom, a lower alkyl group, a lower alkyl group which is substituted by at least one of substituents α, a cycloalkyl group, an aryl group as defined below, or an aralkyl group as defined below;

said aryl group is a carbocyclic aromatic hydrocarbon group having from 6 to 14 carbon atoms in one or more aromatic rings or such a group which is fused to a cycloalkyl group having from 3 to 10 carbon atoms, and the group is unsubstituted or it is substituted by at least one of substituents α or substituents β;

said aralkyl group is a lower alkyl group which is substituted by one or more of the aryl groups defined above;

*t*Bu represents a t-butyl group;

Et represents an ethyl group; and

Ph represents a phenyl group;

said substituents α are selected from hydroxy groups, halogen atoms, lower alkoxy groups and lower alkylthio groups; and

said substituents β are selected from lower alkyl groups, alkanoyloxy groups, mercapto groups, alkanoylthio groups, lower alkylsulphinyl groups, lower alkyl groups which are substituted by at least one of substituents α, cycloalkyloxy groups, lower haloalkoxy groups and lower alkylenedioxy groups;

and pharmaceutically acceptable salts thereof.

[0019] The invention further provides the use of a compound of formula (I) or (II) or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for the treatment or prevention of tumour-related disorders. The compounds may be used to treat or prevent tumours in a mammal, which may be human, in need of such treatment or prevention.

[0020] Preferred classes of compounds of the present invention are those compounds of formula (I) and (II) in which:

(1) R represents a hydrogen atom, a fluorine atom, a chlorine atom or a methyl group, more preferably a hydrogen atom,

(2) R^1 represents a methyl group, an amino group or an acetylamino group, more preferably an amino group or an acetylamino group,

(3) R^2 represents a phenyl group or a phenyl group which is substituted by at least one of substituents α^1 or substituents β^1, more preferably a phenyl group or a phenyl group which is substituted by at least one of substituents α^1 or substituents β^2, still more preferably a phenyl group in which the number of substituents is from 1 to 3,

(4) R^3 represents a hydrogen atom, a halogen atom, a lower alkyl group or a lower alkyl group which is substituted by at least one of substituents α^1, more preferably a hydrogen atom, a halogen atom, a lower alkyl group or a lower alkyl group substituted with a halogen atom,

(5) R^4 represents a hydrogen atom, a lower alkyl group, a lower alkyl group which is substituted by at least one of substituents α, a cycloalkyl group, an aryl group, an aryl group which is substituted by at least one of substituents α^1 or substituents β^3, an aralkyl group or an aralkyl group which is substituted by at least one of substituents α^1 or substituents β^3, more preferably a hydrogen atom, a lower alkyl group, a lower alkyl group which is substituted by at least one of substituents α^2, a cycloalkyl group, an aryl group, an aryl group which is substituted by at least one of substituents α^2 or substituents β^4, an aralkyl group or an aralkyl group which is substituted by at least one

of substituents α^2 or substituents β^4.

[0021] Said substituents α^1 are selected from halogen atoms, lower alkoxy groups and lower alkylthio groups.

[0022] Said substituents α^2 are selected from hydroxy groups, halogen atoms and lower alkoxy groups.

[0023] Said substituents β^1 are selected from lower alkyl groups, mercapto groups, alkanoylthio groups, lower alkyl groups which are substituted by at least one of substituents α^1, lower haloalkoxy groups and lower alkylenedioxy groups.

[0024] Said substituents β^2 are selected from lower alkyl groups, mercapto groups, alkanoylthio groups, lower alkyl groups substituted with a halogen atom, lower haloalkoxy groups and lower alkylenedioxy groups.

[0025] Said substituents β^3 are selected from lower alkyl groups, lower alkyl groups which are substituted by at least one of substituents a and cycloalkyloxy groups.

[0026] Said substituents β^4 are selected from lower alkyl groups, lower alkyl groups substituted with a halogen atom and cycloalkyloxy groups.

[0027] In the compounds of formula (I) and (II), where R, R^3, substituent α, substituent α^1 or substituent α^2 represents a halogen atom, or where substituent β^2 or substituent β^4 represents a lower alkyl group substituted with halogen atom, the halogen atom is preferably a fluorine atom, a chlorine atom, a bromine atom or an iodine atom, preferably a fluorine atom, a chlorine atom or a bromine atom.

[0028] In general, where reference is made herein to a "lower group", unless the context requires otherwise, we mean a group which preferably has no more than 6 carbon atoms in a chain, although, if that group may be substituted, it may be substituted by a group which may contain further carbon atoms.

[0029] Where R, R^1, R^3, R^4, substituent β, substituent β^1, substituent β^2, substituent β^3 or substituent β^4 represents a lower alkyl group, or R^3, R^4, substituent β, substituent β^1 or substituent β^3 represents a lower alkyl group which is substituted by at least one of substituents α, or substituent β^2 or substituent β^4 represents a lower alkyl group substituted with a halogen atom, the alkyl group or alkyl part of the substituted group may be a straight or branched chain alkyl group having from 1 to 6 carbon atoms, and examples include the methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, t-butyl, pentyl, isopentyl, 2-methylbutyl, neopentyl, 1-ethylpropyl, hexyl, isohexyl, 4-methylpentyl, 3-methylpentyl, 2-methylpentyl, 1-methylpentyl, 3,3-dimethylbutyl, 2,2-dimethylbutyl, 1,1-dimethylbutyl, 1,2-dimethylbutyl, 1,3-dimethylbutyl, 2,3-dimethylbutyl and 2-ethylbutyl groups. Of these, we prefer the straight or branched chain alkyl groups having from 1 to 4 carbon atoms, more preferably the methyl and ethyl groups. In R, R^1 and R^4, the lower alkyl group is particularly preferably the methyl group.

[0030] Where substituent β represents an alkanoyloxy group, or substituent β, substituent β^1 or substituent β^2 represents an alkanoylthio group, the alkanoyl part of these groups may be, for example, a straight or branched chain alkanoyl group having from 1 to 25 carbon atoms, such as the formyl, acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, pivaloyl, hexanoyl, heptanoyl, octanoyl, nonanoyl, decanoyl, undecanoyl, lauroyl, tridecanoyl, myristoyl, palmitoyl, stearoyl, icosanoyl, docosanoyl and pentacosanoyl groups. Of these, we prefer those alkanoyl groups having from 1 to 12 carbon atoms, more preferably those alkanoyl groups having from 1 to 6 carbon atoms, still more preferably those alkanoyl groups having from 1 to 4 carbon atoms, and most preferably the acetyl and propionyl groups.

[0031] Where R^4 represents a cycloalkyl group, this is preferably a cycloalkyl group having from 3 to 8 carbon atoms, such as the cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl groups. Of these, we prefer those cycloalkyl group having from 3 to 7 carbon atoms, more preferably those cycloalkyl groups having from 3 to 6 carbon atoms, and most preferably the cyclopropyl group.

[0032] Where R^4 represents an aryl group, this aryl group may be a carbocyclic aromatic hydrocarbon group having from 6 to 14 carbon atoms and may be unsubstituted or it may be substituted by at least one of substituents a or substituents β. The group may contain a single aromatic ring or it may contain two or more fused rings. Examples of such groups include the phenyl, indenyl, naphthyl, phenanthrenyl and anthracenyl groups. Of these, we prefer the phenyl and naphthyl groups, more preferably the phenyl group. The above-mentioned aryl group may be condensed with a cycloalkyl group having from 3 to 10 carbon atoms and examples of such condensed groups include, for example, the 2-indanyl group.

[0033] Where R^4 represents an aralkyl group, this is an alkyl group, which may be any of the alkyl groups defined and exemplified above in relation to R etc., and which is substituted by from 1 to 3 aryl groups, as defined and exemplified above. Such a group may be unsubstituted or it may be substituted by at least one of substituents a or β. Examples of such groups include the benzyl, phenethyl, 3-phenylpropyl, 4-phenylbutyl, 1-naphthylmethyl, 2-naphthylmethyl, diphenylmethyl, triphenylmethyl, 1-naphthyldiphenylmethyl and 9-anthrylmethyl groups. Of these, we prefer an alkyl group having from 1 to 4 carbon atoms which is substituted with one aryl group having from 6 to 10 carbon atoms, preferably substituted by a phenyl group.

[0034] Where substituent α, substituent α^1 or substituent α^2 represents a lower alkoxy group, this may b , for example, a straight or branched chain alkoxy group having from 1 to 6 carbon atoms, such as the methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy, t-butoxy, pentyloxy, isopentyloxy, 2-methylbutoxy, neopentyloxy,

1-ethylpropoxy, hexyloxy, isohexyloxy, 4-methylpentyloxy, 3-methylpentyloxy, 2-methylpentyloxy, 1-methylpentyloxy, 3,3-dimethylbutoxy, 2,2-dimethylbutoxy, 1,1-dimethylbutoxy, 1,2-dimethylbutoxy, 1,3-dimethylbutoxy, 2,3-dimethylbutoxy or 2-ethylbutoxy groups. Of these, we prefer the straight or branched chain alkoxy groups having from 1 to 4 carbon atoms, more preferably the methoxy and ethoxy groups.

[0035] Where substituent α or substituent α^1 represents a lower alkylthio group, this may be a straight or branched chain alkylthio group having from 1 to 6 carbon atoms, and examples include the methylthio, ethylthio, propylthio, isopropylthio, butylthio, isobutylthio, sec-butylthio, t-butylthio, pentylthio, isopentylthio, 2-methylbutylthio, neopentylthio, 1-ethylpropylthio, hexylthio, isohexylthio, 4-methylpentylthio, 3-methylpentylthio, 2-methylpentylthio, 1-methylpentylthio, 3,3-dimethylbutylthio, 2,2-dimethylbutylthio, 1,1-dimethylbutylthio, 1,2-dimethylbutylthio, 1,3-dimethylbutylthio, 2,3-dimethylbutylthio and 2-ethylbutylthio groups. Of these, we prefer the straight or branched chain alkylthio groups having from 1 to 4 carbon atoms, more preferably the methylthio and ethylthio groups.

[0036] Where substituent β represents a lower alkylsulphinyl group, this may be a straight or branched chain alkylsulphinyl group having from 1 to 6 carbon atoms, such as the methylsulphinyl, ethylsulphinyl, propylsulphinyl, isopropylsulphinyl, butylsulphinyl, isobutylsulphinyl, sec-butylsulphinyl, t-butylsulphinyl, pentylsulphinyl, isopentylsulphinyl, 2-methylbutylsulphinyl, neopentylsulphinyl, 1-ethylpropylsulphinyl, hexylsulphinyl, isohexylsulphinyl, 4-methylpentylsulphinyl, 3-methylpentylsulphinyl, 2-methylpentylsulphinyl, 1-methylpentylsulphinyl, 3,3-dimethylbutylsulphinyl, 2,2-dimethylbutylsulphinyl, 1,1-dimethylbutylsulphinyl, 1,2-dimethylbutylsulphinyl, 1,3-dimethylbutylsulphinyl, 2,3-dimethylbutylsulphinyl and 2-ethylbutylsulphinyl groups. Of these, we prefer the straight or branched chain alkylsulphinyl groups having from 1 to 4 carbon atoms.

[0037] Where substituent β, substituent β^3 or substituent β^4 represents a cycloalkyloxy group, this may be, for example, a cycloalkyloxy group having from 3 to 8 carbon atoms, such as the cyclopropyloxy, cyclobutyloxy, cyclopentyloxy, cyclohexyloxy, cycloheptyloxy and cyclooctyloxy groups. Of these, we prefer the cycloalkyloxy groups having from 3 to 7 carbon atoms, more preferably the cycloalkyloxy groups having 5 or 6 carbon atoms, most preferably the cyclopentyloxy group.

[0038] Where substituent β, substituent β^1 or substituent β^2 represents a lower haloalkoxy group, this is an alkoxy group, which may be as defined and exemplified above in relation to substituent a etc., and which is substituted by at least one halogen atom, such as those defined and exemplified above. Examples of such groups include the fluoromethoxy, difluoromethoxy, trifluoromethoxy, 2-fluoroethoxy, 2-chloroethoxy, 2-bromoethoxy, 2,2-difluoroethoxy, 2,2,2-trifluoroethoxy, 2,2,2-trichloroethoxy, 3-fluoropropoxy, 4-fluorobutoxy, chloromethoxy, trichloromethoxy, iodomethoxy and bromomethoxy groups. Of these, we prefer those lower haloalkoxy groups having from 1 to 4 carbon atoms, more preferably the fluoromethoxy, difluoromethoxy, trifluoromethoxy, 2-fluoroethoxy, 2-chloroethoxy, 2-bromoethoxy, 3-fluoropropoxy, 4-fluorobutoxy, chloromethoxy, trichloromethoxy and bromomethoxy groups, and most preferably the fluoromethoxy, difluoromethoxy and trifluoromethoxy groups.

[0039] Where substituent β, substituent β^1 or substituent β^2 represents a lower alkylenedioxy group, this may be, for example, a straight or branched chain alkylenedioxy group having from 1 to 6 carbon atoms, such as the methylenedioxy, ethylenedioxy, trimethylenedioxy, tetramethylenedioxy, pentamethylenedioxy, hexamethylenedioxy and propylenedioxy groups. Of these, we prefer those alkylenedioxy groups having from 1 to 4 carbon atoms, more preferably the methylenedioxy and ethylenedioxy groups.

[0040] Where substituent β^2 or substituent β^4 represents a lower alkyl group substituted with a halogen atom, this may be any of the alkyl groups defined and exemplified above in relation to R etc., which is substituted by at least one halogen atom, as also defined and exemplified above. Examples of such groups include the fluoromethyl, difluoromethyl, trifluoromethyl, 2-fluoroethyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl, 2,2,2-trichloroethyl, 3-fluoropropyl, 4-fluorobutyl, chloromethyl, trichloromethyl, 2-chloroethyl, 3-chloropropyl, bromomethyl, 2-bromoethyl, iodomethyl, 2-iodoethyl, chlorodifluoromethyl and bromodifluoromethyl groups. Of these, we prefer those haloalkyl groups having from 1 to 4 carbon atoms, more preferably the fluoromethyl, difluoromethyl, trifluoromethyl, 2-fluoroethyl, 3-fluoropropyl, 4-fluorobutyl, chloromethyl, trichloromethyl and bromomethyl groups, and most preferably the fluoromethyl, difluoromethyl and trifluoromethyl groups.

[0041] Where R^a represents a group to be eliminated *in vivo* is a group which can be eliminated in the human body under physiological conditions such as hydrolysis, that is a group which can produce a free amino group ($-NH_2$) from a group of formula $-NHR^a$ (in which R^a is as defined above). It is easy to determine whether or not the group can be eliminated *in vivo* by the following test: the compound to be tested is administered orally or intravenously to an experimental animal, such as a rat or mouse, and the body fluid is tested for the presence or absence of the corresponding compound having a free amino group or a pharmaceutically acceptable salt thereof. Such groups include, for example:

the alkanoyl groups defined and exemplified above in relation to substituent β etc.;

a lower alkoxycarbonyl group, in which the alkoxy group is as defined and exemplified above in relation to substituent α etc., such as the methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl,

isobutoxycarbonyl, t-butoxycarbonyl, pentyloxycarbonyl, hexyloxycarbonyl and cyclohexyloxycarbonyl groups;

an aralkyloxycarbonyl group in which the aryl group is as defined above and is unsubstituted or is substituted by one or two lower alkoxy or nitro groups, such as the benzyloxycarbonyl, 4-methoxybenzyloxycarbonyl, 3,4-dimethoxybenzyloxycarbonyl, 2-nitrobenzyloxycarbonyl and 4-nitrobenzyloxycarbonyl groups;

an alkanoyloxymethyl group in which the alkanoyl group is as defined and exemplified above in relation to substituent β etc., such as the formyloxymethyl, acetoxymethyl, propionyloxymethyl, butyryloxymethyl, pivaloyloxymethyl, valeryloxymethyl, isovaleryloxymethyl and hexanoyloxymethyl groups;

a lower alkoxycarbonyloxymethyl group in which the alkoxy group is as defined and exemplified above in relation to substituent α etc., such as the methoxycarbonyloxymethyl, ethoxycarbonyloxymethyl, propoxycarbonyloxymethyl, isopropoxycarbonyloxymethyl, butoxycarbonyloxymethyl, isobutoxycarbonyloxymethyl and pentyloxycarbonyloxymethyl groups; and

a (2-oxo-1,3-dioxolen-4-yl)methyl group in which the 5-position of the dioxolene ring may be substituted with a lower alkyl group or an aryl group, as defined and exemplified above in relation to R and R^4, respectively, such as the (5-phenyl-2-oxo-1,3-dioxolen-4-yl)methyl, [5-(4-methylphenyl)-2-oxo-1,3-dioxolen-4-yl]methyl, [5-(4-methoxyphenyl)-2-oxo-1,3-dioxolen-4-yl]methyl, [5-(4-fluorophenyl)-2-oxo-1,3-dioxolen-4-yl]methyl, [5-(4-chlorophenyl)-2-oxo-1,3-dioxolen-4-yl]methyl, (2-oxo-1,3-dioxolen-4-yl)methyl, (5-methyl-2-oxo-1,3-dioxolen-4-yl)methyl, (5-ethyl-2-oxo-1,3-dioxolen-4-yl)methyl, (5-propyl-2-oxo-1,3-dioxolen-4-yl)methyl, (5-isopropyl-2-oxo-1,3-dioxolen-4-yl)methyl and (5-butyl-2-oxo-1,3-dioxolen-4-yl)methyl groups.

[0042] Of these, we prefer the alkanoyl groups having from 1 to 12 carbon atoms, the alkoxycarbonyl groups having from 2 to 5 carbon atoms, the aralkyloxycarbonyl groups having 7 or 8 carbon atoms, the alkanoyloxymethyl groups having from 3 to 6 carbon atoms, the alkoxycarbonyloxymethyl groups having from 3 to 6 carbon atoms and the 5-substituted (2-oxo-1,3-dioxolen-4-yl)methyl group, more preferably the acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, pivaloyl, methoxycarbonyl, ethoxycarbonyl, benzyloxycarbonyl, acetoxymethyl, propionyloxymethyl, methoxycarbonyloxymethyl, ethoxycarbonyloxymethyl, (5-methyl-2-oxo-1,3-dioxolen-4-yl)methyl and (5-phenyl-2-oxo-1,3-dioxolen-4-yl)methyl groups, and most preferably the acetyl group.

[0043] Specific examples of R^1 preferably include the methyl, ethyl, amino, acetylamino, propionylamino, butyrylamino, isobutyrylamino, valerylamino, isovalerylamino, pivaloylamino, methoxycarbonylamino, ethoxycarbonylamino, benzyloxycarbonylamino, acetoxymethylamino, propionyloxymethylamino, methoxycarbonyloxymethylamino, ethoxycarbonyloxymethylamino, (5-methyl-2-oxo-1,3-dioxolen-4-yl)methylamino and (5-phenyl-2-oxo-1,3-dioxolen-4-yl)methylamino groups, more preferably the methyl, amino and acetylamino groups, and most preferably the amino and acetylamino groups.

[0044] Specific examples of R^2 preferably include:

the unsubstituted phenyl group;

phenyl groups having from 1 to 3 substituents selected from mercapto groups, C_1 - C_4 alkanoylthio groups, halogen atoms, C_1 - C_4 alkyl groups, C_1 - C_4 alkoxy groups, C_1 - C_4 alkylthio groups and C_1 - C_4 alkylsulphinyl groups, such as the 4-mercaptophenyl, 4-acetylthiophenyl, 4-propionylthiophenyl, 4-fluorophenyl, 4-chlorophenyl, 4-bromophenyl, p-tolyl, 4-ethylphenyl, 4-methoxyphenyl, 4-ethoxyphenyl, 4-methylthiophenyl, 4-ethylthiophenyl, 4-methylsulphinylphenyl, 4-ethylsulphinylphenyl, 3,4-difluorophenyl, 2,4-difluorophenyl, 3,4-dichlorophenyl, 2,4-dichlorophenyl, 3,4-dimethylphenyl, 3,4-dimethoxyphenyl, 3-chloro-4-fluorophenyl, 3-chloro-4-methoxyphenyl, 3-fluoro-4-methoxyphenyl, 3-methyl-4-methoxyphenyl, 3,5-dichloro-4-methoxyphenyl and 4-methoxy-3,5-dimethylphenyl groups;

trifluoromethyl-, difluoromethoxy- or trifluoromethoxy-substituted phenyl groups, such as the 4-trifluoromethylphenyl, 4-difluoromethoxyphenyl and 4-trifluoromethoxyphenyl groups;

methylenedioxy- or ethylenedioxy-substituted phenyl group such as the 3,4-methylenedioxyphenyl and 3,4-ethylenedioxyphenyl groups.

[0045] In the case where R^2 is a substitut d phenyl group, the number of substituents is preferably from 1 to 3, more preferably 1 or 2.

[0046] Specific examples of R^3 preferably include hydrogen atoms; halogen atoms, such as the fluorin , chlorine,

bromine and iodine atoms; C_1 - C_4 alkyl groups, such as the methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl and t-butyl groups; and C_1 - C_4 haloalkyl groups, such as the fluoromethyl, chloromethyl, bromomethyl, iodomethyl, difluoromethyl, trifluoromethyl, 2-fluoroethyl, 3-fluoropropyl, 4-fluorobutyl, 2-chloroethyl and 3-chloropropyl groups, more preferably hydrogen atoms; halogen atoms, such as the fluorine, chlorine, bromine and iodine atoms; and the methyl, ethyl, fluoromethyl, difluoromethyl, 2-fluoroethyl and 2-chloroethyl groups.

[0047] Specific examples of R^4 preferably include hydrogen atoms; C_1 - C_6 alkyl groups, such as the methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, t-butyl, pentyl and hexyl groups; any of these alkyl groups optionally having a substituent selected from hydroxy, halogen (such as fluorine, chlorine, bromine or iodine) and C_1 - C_4 alkoxy (such as methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy and t-butoxy); C_3 - C_7 cycloalkyl groups, such as the cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl groups; C_6 - C_{10} aryl groups, such as the phenyl and naphthyl groups, which may be unsubstituted or may have one or more of the following substituents γ; C_6 - C_{10} aryl C_1 - C_4 alkyl groups, such as the benzyl, phenethyl, 3-phenylpropyl, 4-phenylbutyl, 1-naphthylmethyl and 2-naphthylmethyl groups, which may be unsubstituted or may have one or more of the following substituents y in the aryl moiety;

substituents γ include: halogen atoms, such as the fluorine, chlorine, bromine and iodine atoms; C_1 - C_4 alkyl groups, such as the methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl and t-butyl groups; C_1 - C_4 haloalkyl groups, such as the fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, trichloromethyl, chlorodifluoromethyl, 2-fluoroethyl, 2-chloroethyl, 2-bromoethyl, 2-iodoethyl, 3-fluoropropyl and 4-fluoropropyl groups; C_1 - C_4 alkoxy groups, such as the methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy and t-butoxy groups; and C_3 - C_7 cycloalkyloxy groups, such as the cyclopropyloxy, cyclobutyloxy, cyclopentyloxy, cyclohexyloxy and cycloheptyloxy groups.

[0048] Preferred examples of R^4 include: hydrogen atoms; C_1 - C_4 alkyl groups, such as the methyl, ethyl, isopropyl, butyl and isobutyl groups; C_1 - C_4 mono-, di- or trihaloalkyl groups, such as the fluoromethyl, difluoromethyl, chlorodifluoromethyl, bromodifluoromethyl, trifluoromethyl, 2-fluoroethyl and 2,2,2-trifluoroethyl groups; hydroxymethyl groups; C_1 - C_4 alkoxymethyl groups, such as the methoxymethyl and ethoxymethyl groups; C_3 - C_6 cycloalkyl groups, such as the cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl groups; phenyl groups; mono- or difluorophenyl groups, such as the 4-fluorophenyl and 2,4-difluorophenyl groups; mono- or dimethoxyphenyl groups, such as the 4-methoxyphenyl and 3,4-dimethoxyphenyl groups; tolyl groups, such as the p-tolyl and o-tolyl groups; cyclopentyloxy-(methoxy) phenyl groups, such as the 3-cyclopentyloxy-4-methoxyphenyl group; trifluoromethylphenyl groups, such as the 4-trifluoromethylphenyl group; benzyl groups; substituted benzyl groups, such as the 4-methoxybenzyl and 3-cyclopentyloxy-4-methoxybenzyl groups; phenethyl groups; naphthyl groups, such as the 1-naphthyl and 2-naphthyl groups; and naphthylmethyl groups, such as the 1-naphthylmethyl and 2-naphthylmethyl groups.

[0049] Certain of the compounds of the present invention, specifically the compounds of formula (I) and (II), possess an acidic group and can thus form salts with cations. The nature of the salt is not critical to the present invention, provided that it is pharmaceutically acceptable, that is that the salt is neither less active (or unacceptably less active) nor more toxic (or unacceptably more toxic) than the free acid. Such salts include, for example: salts with alkali metals, such as sodium, potassium or lithium; salts with alkaline earth metals, such as calcium or magnesium; salts with other metals, such as aluminium, iron, zinc, copper, nickel or cobalt; other inorganic salts, such as the ammonium salt; salts with organic amines, such as t-octylamine, dibenzylamine, morpholine, glucosamine, phenylglycine alkyl ester, ethylenediamine, N-methylglucamine, guanidine, diethylamine, triethylamine, dicyclohexylamine, N,N'-dibenzylethylenediamine, chloroprocaine, procaine, diethanolamine, N-benzyl-N-phenethylamine, piperazine, tetramethyl ammonium or tris(hydroxymethyl)aminomethane.

[0050] Further, when the compounds of formula (I) and (II) and salts thereof are allowed to stand in the atmosphere, they may adsorb moisture to form hydrates. Such hydrates are also included in the present invention.

[0051] Further, the compounds of formula (I) and (II) and salts thereof sometimes absorb certain kinds of solvents to afford solvates, and such solvates are also included in the present invention.

[0052] Certain of the compounds of formula (I) and (II) of the present invention may have asymmetric carbon atoms in their molecule, and stereoisomers in the R-configuration or the S-configuration would then exist. Each of these stereoisomers and mixtures thereof in any desired proportion are all included in the present invention.

[0053] Specific examples of the compounds of formula (I) and (II) employed in the method and composition of the present invention include, for example, those shown in the following Table 1 [compounds of formula (I)] and Table 2 [compounds of formula (II)].

[0054] In the Tables, the following abbreviations are used:

Ac acetyl;
Bu butyl;
Byr butyryl;
iByr isobutyryl;

Bz	benzyl;
Et	ethyl;
For	formyl;
Me	methyl;
Ph	phenyl;
Piv	pivaloyl;
cPn	cyclopentyl;
Pr	propyl;
cPr	cyclopropyl;
iPr	isopropyl;
Prn	propionyl;
iVal	isovaleryl; and
Val	valeryl.

Table 1

Cpd. No.	R	R^1	R^2	R^3	R^4
1-1	H	Me	Ph	H	H
1-2	H	Me	Ph	H	Me
1-3	H	Me	4-F-Ph	H	H
1-4	H	Me	4-F-Ph	F	H
1-5	H	Me	4-F-Ph	Cl	H
1-6	H	Me	4-F-Ph	Br	H
1-7	H	Me	4-F-Ph	I	H
1-8	H	Me	4-F-Ph	Me	H
1-9	H	Me	4-F-Ph	Et	H
1-10	H	Me	4-F-Ph	Pr	H
1-11	H	Me	4-F-Ph	Bu	H
1-12	H	Me	4-F-Ph	CH_2F	H
1-13	H	Me	4-F-Ph	CHF_2	H
1-14	H	Me	4-F-Ph	CF_3	H
1-15	H	Me	4-F-Ph	H	Me
1-16	H	Me	4-F-Ph	F	Me
1-17	H	Me	4-F-Ph	Cl	Me
1-18	H	Me	4-F-Ph	Br	Me
1-19	H	Me	4-F-Ph	I	Me
1-20	H	Me	4-F-Ph	Me	Me
1-21	H	Me	4-F-Ph	Et	Me
1-22	H	Me	4-F-Ph	Pr	Me
1-23	H	Me	4-F-Ph	H	Et
1-24	H	Me	4-F-Ph	H	Pr
1-25	H	Me	4-F-Ph	H	Bu
1-26	H	Me	4-F-Ph	H	cPr
1-27	H	Me	4-F-Ph	H	Ph
1-28	H	Me	4-F-Ph	H	CH_2Ph

Table 1 (continued)

Cpd. No.	R	R^1	R^2	R^3	R^4
1-29	H	Me	4-F-Ph	H	CHF_2
1-30	H	Me	4-F-Ph	Me	CHF_2
1-31	H	Me	4-F-Ph	H	CF_3
1-32	H	Me	4-F-Ph	Me	CF_3
1-33	H	Me	4-MeO-Ph	H	H
1-34	H	Me	4-MeO-Ph	H	Me
1-35	H	Me	4-Cl-Ph	H	H
1-36	H	Me	4-Cl-Ph	H	Me
1-37	H	Me	4-Me-Ph	H	H
1-38	H	Me	4-Me-Ph	H	Me
1-39	H	Me	3-Cl-4-F-Ph	H	H
1-40	H	Me	3-Cl-4-F-Ph	H	Me
1-41	H	Me	3,4-methylenedioxy-Ph	H	H
1-42	H	Me	3,4-methylenedioxy-Ph	H	Me
1-43	H	Me	3-Cl-4-MeO-Ph	H	H
1-44	H	Me	3-Cl-4-MeO-Ph	H	Me
1-45	H	Me	4-CF_3-Ph	H	H
1-46	H	Me	4-CF_3O-Ph	H	H
1-47	H	Me	3-F-4-MeO-Ph	H	H
1-48	H	Me	3-F-4-MeO-Ph	H	Me
1-49	H	Me	3-Me-4-MeO-Ph	H	H
1-50	H	Me	3-Me-4-MeO-Ph	H	Me
1-51	H	Me	3,4-diF-Ph	H	H
1-52	H	Me	3,4-diF-Ph	H	Me
1-53	H	Me	2,4-diF-Ph	H	H
1-54	H	Me	2,4-diF-Ph	H	Me
1-55	H	Me	3,4-diMe-Ph	H	H
1-56	H	Me	3,4-diMe-Ph	H	Me
1-57	H	Me	3,4-diCl-Ph	H	H
1-58	H	Me	3,4-diCl-Ph	H	Me
1-59	H	Me	3,4-di(MeO)-Ph	H	H
1-60	H	Me	3,4-di(MeO)-Ph	H	Me
1-61	H	Me	4-F-Ph	H	CH_2OH
1-62	H	Me	4-F-Ph	Me	CH_2OH
1-63	H	Me	4-F-Ph	H	CH_2OMe
1-64	H	Me	4-MeO-Ph	H	CH_2OH
1-65	H	Me	4-MeO-Ph	H	CH_2OMe
1-66	H	Me	4-Cl-Ph	H	CH_2OH

Table 1 (continued)

Cpd. No.	R	R^1	R^2	R^3	R^4
1-67	H	Me	4-Cl-Ph	H	CH_2OMe
1-68	H	Me	4-Me-Ph	H	CH_2OH
1-69	H	Me	4-Me-Ph	H	CH_2OMe
1-70	H	NH_2	Ph	H	H
1-71	H	NH_2	Ph	H	Me
1-72	H	NH_2	Ph	Me	H
1-73	H	NH_2	4-F-Ph	H	H
1-74	H	NH_2	4-F-Ph	H	Me
1-75	H	NH_2	4-F-Ph	Cl	Me
1-76	H	NH_2	4-F-Ph	Me	H
1-77	H	NH_2	4-F-Ph	H	Et
1-78	H	NH_2	4-F-Ph	H	Pr
1-79	H	NH_2	4-F-Ph	H	Bu
1-80	H	NH_2	4-F-Ph	H	cPr
1-81	H	NH_2	4-F-Ph	H	Ph
1-82	H	NH_2	4-F-Ph	H	CH_2Ph
1-83	H	NH_2	4-F-Ph	H	CHF_2
1-84	H	NH_2	4-F-Ph	H	CF_3
1-85	H	NH_2	4-MeO-Ph	H	H
1-86	H	NH_2	4-MeO-Ph	H	Me
1-87	H	NH_2	4-MeO-Ph	H	Bu
1-88	H	NH_2	4-MeO-Ph	Me	H
1-89	H	NH_2	4-EtO-Ph	H	H
1-90	H	NH_2	4-EtO-Ph	H	Me
1-91	H	NH_2	4-EtO-Ph	Me	H
1-92	H	NH_2	4-PrO-Ph	H	Me
1-93	H	NH_2	4-MeS-Ph	H	H
1-94	H	NH_2	4-MeS-Ph	H	Me
1-95	H	NH_2	4-MeS-Ph	Me	H
1-96	H	NH_2	4-Cl-Ph	H	H
1-97	H	NH_2	4-Cl-Ph	H	Me
1-98	H	NH_2	4-Cl-Ph	Me	H
1-99	H	NH_2	4-Me-Ph	H	H
1-100	H	NH_2	4-Me-Ph	H	Me
1-101	H	NH_2	4-Me-Ph	Me	H
1-102	H	NH_2	3-Cl-4-F-Ph	H	H
1-103	H	NH_2	3-Cl-4-F-Ph	H	Me
1-104	H	NH_2	3-Cl-4-F-Ph	Me	H

Table 1 (continued)

Cpd. No.	R	R^1	R^2	R^3	R^4
1-105	H	NH_2	3,4-methylenedioxy-Ph	H	H
1-106	H	NH_2	3,4-methylenedioxy-Ph	H	Me
1-107	H	NH_2	3-Cl-4-MeO-Ph	H	H
1-108	H	NH_2	3-Cl-4-MeO-Ph	H	Me
1-109	H	NH_2	3-Cl-4-MeO-Ph	Me	H
1-110	H	NH_2	4-CF_3-Ph	H	H
1-111	H	NH_2	4-CF_3O-Ph	H	H
1-112	H	NH_2	3-F-4-MeO-Ph	H	H
1-113	H	NH_2	3-F-4-MeO-Ph	H	Me
1-114	H	NH_2	3-F-4-MeO-Ph	Me	H
1-115	H	NH_2	3-Me-4-MeO-Ph	H	H
1-116	H	NH_2	3-Me-4-MeO-Ph	H	Me
1-117	H	NH_2	3-Me-4-MeO-Ph	Me	H
1-118	H	NH_2	3,4-diF-Ph	H	H
1-119	H	NH_2	3,4-diF-Ph	H	Me
1-120	H	NH_2	3,4-diF-Ph	Me	H
1-121	H	NH_2	2,4-diF-Ph	H	H
1-122	H	NH_2	2,4-diF-Ph	H	Me
1-123	H	NH_2	2,4-diF-Ph	Me	H
1-124	H	NH_2	3,4-diMe-Ph	H	H
1-125	H	NH_2	3,4-diMe-Ph	H	Me
1-126	H	NH_2	3,4-diMe-Ph	Me	H
1-127	H	NH_2	2,4-diCl-Ph	H	H
1-128	H	NH_2	2,4-diCl-Ph	H	Me
1-129	H	NH_2	2,4-diCl-Ph	Me	H
1-130	H	NH_2	3,4-diCl-Ph	H	H
1-131	H	NH_2	3,4-diCl-Ph	H	Me
1-132	H	NH_2	3,4-diCl-Ph	Me	H
1-133	H	NH_2	3,4-di(MeO)-Ph	H	H
1-134	H	NH_2	3,4-di(MeO)-Ph	H	Me
1-135	H	NH_2	4-F-Ph	H	CH_2OH
1-136	H	NH_2	4-F-Ph	H	CH_2OMe
1-137	H	NH_2	4-MeO-Ph	H	CH_2OH
1-138	H	NH_2	4-MeO-Ph	H	CH_2OMe
1-139	H	NH_2	4-Cl-Ph	H	CH_2OH
1-140	H	NH_2	4-Cl-Ph	H	CH_2OMe
1-141	H	NH_2	4-Me-Ph	H	CH_2OH
1-142	H	NH_2	4-Me-Ph	H	CH_2OMe

Table 1 (continued)

Cpd. No.	R	R^1	R^2	R^3	R^4
1-143	H	NH_2	4-Et-Ph	H	H
1-144	H	NH_2	4-Et-Ph	H	Me
1-145	H	NH_2	4-Et-Ph	Me	H
1-146	H	NH_2	2,4,6-triMe-Ph	H	Me
1-147	H	NH_2	4-MeO-Ph	Cl	H
1-148	H	NH_2	4-MeO-Ph	Br	H
1-149	H	NH_2	4-MeO-Ph	Cl	Me
1-150	H	NH_2	2-F-4-Cl-Ph	H	Me
1-151	H	NH_2	4-EtO-Ph	Cl	H
1-152	H	NH_2	4-MeS-Ph	Cl	H
1-153	H	NH_2	4-MeSO-Ph	H	Me
1-154	H	NH_2	4-EtS-Ph	H	Me
1-155	H	NH_2	2,4-diCl-Ph	Cl	H
1-156	H	NH_2	4-SH-Ph	H	Me
1-157	H	NH_2	4-AcS-Ph	H	Me
1-158	3-F	NH_2	4-MeO-Ph	H	Me
1-159	3-F	NH_2	4-EtO-Ph	H	Me
1-160	3-F	NH_2	3,4-diMe-Ph	H	Me
1-161	3-F	NH_2	4-Cl-Ph	H	Me
1-162	3-F	NH_2	4-F-Ph	H	Me
1-163	3-F	NH_2	4-SH-Ph	H	Me
1-164	3-F	NH_2	4-MeS-Ph	H	Me
1-165	3-F	NH_2	4-EtS-Ph	H	Me
1-166	3-F	NH_2	4-AcS-Ph	H	Me
1-167	3-Me	NH_2	4-MeO-Ph	H	Me
1-168	3-Me	NH_2	4-EtO-Ph	H	Me
1-169	3-Me	NH_2	3,4-diMe-Ph	H	Me
1-170	3-Me	NH_2	4-Cl-Ph	H	Me
1-171	3-Me	NH_2	4-F-Ph	H	Me
1-172	3-Me	NH_2	4-MeS-Ph	H	Me
1-173	H	NHFor	4-MeS-Ph	H	Me
1-174	H	NHAc	4-MeS-Ph	H	Me
1-175	H	NHPrn	4-MeS-Ph	H	Me
1-176	H	NHByr	4-MeS-Ph	H	Me
1-177	H	NHiByr	4-MeS-Ph	H	Me
1-178	H	NHVal	4-MeS-Ph	H	Me
1-179	H	NHiVal	4-MeS-Ph	H	Me
1-180	H	NHPiv	4-MeS-Ph	H	Me

Table 1 (continued)

Cpd. No.	R	R^1	R^2	R^3	R^4
1-181	H	NH(MeOCO)	4-MeS-Ph	H	Me
1-182	H	NH(EtOCO)	4-MeS-Ph	H	Me
1-183	H	NH(BzOCO)	4-MeS-Ph	H	Me
1-184	H	NH($AcOCH_2$)	4-MeS-Ph	H	Me
1-185	H	NH($PmOCH_2$)	4-MeS-Ph	H	Me
1-186	H	NH($MeOCOOCH_2$)	4-MeS-Ph	H	Me
1-187	H	NH($EtOCOOCH_2$)	4-MeS-Ph	H	Me
1-188	H	NH[(5-Me-2-oxo-1,3-dioxolen-4-yl)CH_2]	4-MeS-Ph	H	Me
1-189	H	NH[(5-Ph-2-oxo-1,3-dioxolen-4-yl)CH_2]	4-MeS-Ph	H	Me

Table 2

Cpd. No.	R	R^1	R^2	R^3	R^4
2-1	H	Me	Ph	H	H
2-2	H	Me	Ph	H	Me
2-3	H	Me	4-F-Ph	H	H
2-4	H	Me	4-F-Ph	F	H
2-5	H	Me	4-F-Ph	Cl	H
2-6	H	Me	4-F-Ph	Br	H
2-7	H	Me	4-F-Ph	I	H
2-8	H	Me	4-F-Ph	Me	H
2-9	H	Me	4-F-Ph	Et	H
2-10	H	Me	4-F-Ph	Pr	H
2-11	H	Me	4-F-Ph	H	Me
2-12	H	Me	4-F-Ph	H	Et
2-13	H	Me	4-F-Ph	H	Pr
2-14	H	Me	4-F-Ph	H	Bu
2-15	H	Me	4-F-Ph	H	cPr
2-16	H	Me	4-F-Ph	H	Ph
2-17	H	Me	4-F-Ph	H	CH_2Ph
2-18	H	Me	4-F-Ph	H	CHF_2
2-19	H	Me	4-F-Ph	H	CF_3
2-20	H	Me	4-MeO-Ph	H	H
2-21	H	Me	4-MeO-Ph	Me	H
2-22	H	Me	4-MeO-Ph	H	Me
2-23	H	Me	4-Cl-Ph	H	H
2-24	H	Me	4-Cl-Ph	Me	H
2-25	H	Me	4-Me-Ph	H	H

Table 2 (continued)

Cpd. No.	R	R^1	R^2	R^3	R^4
2-26	H	Me	4-Me-Ph	Me	H
2-27	H	Me	4-Me-Ph	H	Me
2-28	H	Me	3-Cl-4-F-Ph	H	H
2-29	H	Me	3-Cl-4-F-Ph	H	Me
2-30	H	Me	3,4-Methylenedioxy-Ph	H	H
2-31	H	Me	3,4-Methylenedioxy-Ph	H	Me
2-32	H	Me	3-Cl-4-MeO-Ph	H	H
2-33	H	Me	3-Cl-4-MeO-Ph	H	Me
2-34	H	Me	4-CF_3-Ph	H	H
2-35	H	Me	4-CF_3O-Ph	H	H
2-36	H	Me	4-CHF_2O-Ph	H	H
2-37	H	Me	4-CHF_2O-Ph	Me	H
2-38	H	Me	3-F-4-MeO-Ph	H	H
2-39	H	Me	3-F-4-MeO-Ph	H	Me
2-40	H	Me	3-Me-4-MeO-Ph	H	H
2-41	H	Me	3-Me-4-MeO-Ph	H	Me
2-42	H	Me	3,4-diF-Ph	H	H
2-43	H	Me	3,4-diF-Ph	H	Me
2-44	H	Me	2,4-diF-Ph	H	H
2-45	H	Me	2,4-diF-Ph	H	Me
2-46	H	Me	3,4-diMe-Ph	H	H
2-47	H	Me	3,4-diCl-Ph	H	H
2-48	H	Me	3,4-diCl-Ph	H	Me
2-49	H	Me	3,4-di(MeO)-Ph	H	H
2-50	H	Me	3,4-di(MeO)-Ph	H	Me
2-51	H	Me	4-F-Ph	H	CH_2OH
2-52	H	Me	4-F-Ph	H	CH_2OMe
2-53	H	Me	4-MeO-Ph	H	CH_2OH
2-54	H	Me	4-MeO-Ph	H	CH_2OMe
2-55	H	Me	4-Cl-Ph	H	CH_2OH
2-56	H	Me	4-Cl-Ph	H	CH_2OMe
2-57	H	Me	4-Me-Ph	H	CH_2OH
2-58	H	Me	4-Me-Ph	H	CH_2OMe
2-59	H	NH_2	Ph	H	H
2-60	H	NH_2	Ph	H	Me
2-61	H	NH_2	Ph	Me	H
2-62	H	NH_2	4-F-Ph	H	H

Table 2 (continued)

Cpd. No.	R	R^1	R^2	R^3	R^4
2-63	H	NH_2	4-F-Ph	H	Me
2-64	H	NH_2	4-F-Ph	Me	H
2-65	H	NH_2	4-F-Ph	H	Et
2-66	H	NH_2	4-F-Ph	H	Pr
2-67	H	NH_2	4-F-Ph	H	Bu
2-68	H	NH_2	4-F-Ph	H	cPr
2-69	H	NH_2	4-F-Ph	H	Ph
2-70	H	NH_2	4-F-Ph	H	CH_2Ph
2-71	H	NH_2	4-F-Ph	H	CHF_2
2-72	H	NH_2	4-F-Ph	H	CF_3
2-73	H	NH_2	4-MeO-Ph	H	H
2-74	H	NH_2	4-MeO-Ph	H	Me
2-75	H	NH_2	4-MeO-Ph	H	Et
2-76	H	NH_2	4-MeO-Ph	Me	H
2-77	H	NH_2	4-EtO-Ph	H	H
2-78	H	NH_2	4-EtO-Ph	H	Me
2-79	H	NH_2	4-EtO-Ph	Me	H
2-80	H	NH_2	4-PrO-Ph	H	Me
2-81	H	NH_2	4-MeS-Ph	H	H
2-82	H	NH_2	4-MeS-Ph	H	Me
2-83	H	NH_2	4-MeS-Ph	Me	H
2-84	H	NH_2	4-Cl-Ph	H	H
2-85	H	NH_2	4-Cl-Ph	H	Me
2-86	H	NH_2	4-Cl-Ph	Me	H
2-87	H	NH_2	4-Me-Ph	H	H
2-88	H	NH_2	4-Me-Ph	Me	H
2-89	H	NH_2	4-Me-Ph	H	Me
2-90	H	NH_2	4-Et-Ph	H	H
2-91	H	NH_2	4-Et-Ph	H	Me
2-92	H	NH_2	4-Et-Ph	Me	H
2-93	H	NH_2	4-iPr-Ph	H	Me
2-94	H	NH_2	3-Cl-4-F-Ph	H	H
2-95	H	NH_2	3-Cl-4-F-Ph	H	Me
2-96	H	NH_2	3-Cl-4-F-Ph	Me	H
2-97	H	NH_2	3,4-Methylenedioxy-Ph	H	H
2-98	H	NH_2	3,4-Methylenedioxy-Ph	H	Me
2-99	H	NH_2	3-Cl-4-MeO-Ph	H	H

Table 2 (continued)

Cpd. No.	R	R^1	R^2	R^3	R^4
2-100	H	NH_2	3-Cl-4-MeO-Ph	H	Me
2-101	H	NH_2	3-Cl-4-MeO-Ph	Me	H
2-102	H	NH_2	4-CF_3-Ph	H	Me
2-103	H	NH_2	4-CHF_2O-Ph	H	Me
2-104	H	NH_2	4-CF_3O-Ph	H	Me
2-105	H	NH_2	2-F-4-MeO-Ph	H	Me
2-106	H	NH_2	3-F-4-MeO-Ph	H	Me
2-107	H	NH_2	3-F-4-MeO-Ph	Me	H
2-108	H	NH_2	3-Me-4-MeO-Ph	H	H
2-109	H	NH_2	3-Me-4-MeO-Ph	H	Me
2-110	H	NH_2	3-Me-4-MeO-Ph	Me	H
2-111	H	NH_2	3,4-diF-Ph	H	H
2-112	H	NH_2	3,4-diF-Ph	H	Me
2-113	H	NH_2	3,4-diF-Ph	Me	H
2-114	H	NH_2	2,4-diF-Ph	H	H
2-115	H	NH_2	2,4-diF-Ph	H	Me
2-116	H	NH_2	2,4-diF-Ph	Me	H
2-117	H	NH_2	3,4-diMe-Ph	H	H
2-118	H	NH_2	3,4-diMe-Ph	H	Me
2-119	H	NH_2	3,4-diMe-Ph	Me	H
2-120	H	NH_2	2,4-diCl-Ph	H	H
2-121	H	NH_2	2,4-diCl-Ph	H	Me
2-122	H	NH_2	2,4-diCl-Ph	Me	H
2-123	H	NH_2	3,4-diCl-Ph	H	H
2-124	H	NH_2	3,4-diCl-Ph	H	Me
2-125	H	NH_2	3,4-diCl-Ph	Me	H
2-126	H	NH_2	3,4-di(MeO)-Ph	H	H
2-127	H	NH_2	3,4-di(MeO)-Ph	H	Me
2-128	H	NH_2	4-F-Ph	H	CH_2OH
2-129	H	NH_2	4-F-Ph	H	CH_2OMe
2-130	H	NH_2	4-MeO-Ph	H	CH_2OH
2-131	H	NH_2	4-MeO-Ph	H	CH_2OMe
2-132	H	NH_2	4-Cl-Ph	H	CH_2OH
2-133	H	NH_2	4-Cl-Ph	H	CH_2OMe
2-134	H	NH_2	4-Me-Ph	H	CH_2OH
2-135	H	NH_2	4-Me-Ph	H	CH_2OMe
2-136	H	NH_2	3,5-diCl-4-MeO-Ph	H	Me

Table 2 (continued)

Cpd. No.	R	R^1	R^2	R^3	R^4
2-137	H	NH_2	3,5-diMe-4-MeO-Ph	H	Me
2-138	H	NH_2	2,3-diCl-Ph	H	Me
2-139	H	NH_2	3,5-diCl-Ph	H	Me
2-140	H	NH_2	2,4,5-triMe-Ph	H	Me
2-141	H	NH_2	3-cPnO-4-MeO-Ph	H	Me
2-142	H	NH_2	3-CF_3-4-Cl-Ph	H	Me
2-143	H	NH_2	3-F-4-Me-Ph	H	Me
2-144	H	NH_2	3-Me-4-Cl-Ph	H	Me
2-145	H	NH_2	2,4-diMe-Ph	H	Me
2-146	H	NH_2	4-OH-Ph	H	Me
2-147	H	NH_2	3,5-diMe-Ph	H	Me
2-148	H	NHAc	4-MeO-Ph	H	Me
2-149	H	NHAc	3,4-diMe-Ph	H	Me
2-150	H	NH_2	4-MeO-Ph	H	3-cPnO-4-MeO-Bz
2-151	H	NH_2	4-MeSO-Ph	H	Me
2-152	3-F	NH_2	4-MeO-Ph	H	Me
2-153	3-F	NH_2	4-EtO-Ph	H	Me
2-154	3-F	NH_2	3,4-diMe-Ph	H	Me
2-155	3-F	NH_2	4-Cl-Ph	H	Me
2-156	3-F	NH_2	4-F-Ph	H	Me
2-157	3-F	NH_2	4-SH-Ph	H	Me
2-158	3-F	NH_2	4-MeS-Ph	H	Me
2-159	3-F	NH_2	4-EtS-Ph	H	Me
2-160	3-F	NH_2	4-AcS-Ph	H	Me
2-161	3-Me	NH_2	4-MeO-Ph	H	Me
2-162	3-Me	NH_2	4-EtO-Ph	H	Me
2-163	3-Me	NH_2	3,4-diMe-Ph	H	Me
2-164	3-Me	NH_2	4-MeS-Ph	H	Me
2-165	H	NHFor	4-MeO-Ph	H	Me
2-166	H	NHPrn	4-MeO-Ph	H	Me
2-167	H	NHByr	4-MeO-Ph	H	Me
2-168	H	NHiByr	4-MeO-Ph	H	Me
2-169	H	NHVal	4-MeO-Ph	H	Me
2-170	H	NHiVal	4-MeO-Ph	H	Me
2-171	H	NHPiv	4-MeO-Ph	H	Me
2-172	H	NH(MeOCO)	4-MeO-Ph	H	Me
2-173	H	NH(EtOCO)	4-MeO-Ph	H	Me

Table 2 (continued)

Cpd. No.	R	R^1	R^2	R^3	R^4
2-174	H	NH(BzOCO)	4-MeO-Ph	H	Me
2-175	H	NH($AcOCH_2$)	4-MeO-Ph	H	Me
2-176	H	NH($PmOCH_2$)	4-MeO-Ph	H	Me
2-177	H	NH($MeOCOOCH_2$)	4-MeO-Ph	H	Me
2-178	H	NH($EtOCOOCH_2$)	4-MeO-Ph	H	Me
2-179	H	NH[(5-Me-2-oxo-1,3-dioxolen-4-yl) CH_2]	4-MeO-Ph	H	Me
2-180	H	NH[(5-Ph-2-oxo-1,3-dioxolen-4-yl) CH_2]	4-MeO-Ph	H	Me
2-181	H	NHFor	4-EtO-Ph	H	Me
2-182	H	NHAc	4-EtO-Ph	H	Me
2-183	H	NHPrn	4-EtO-Ph	H	Me
2-184	H	NHByr	4-EtO-Ph	H	Me
2-185	H	NHiByr	4-EtO-Ph	H	Me
2-186	H	NHVal	4-EtO-Ph	H	Me
2-187	H	NHiVal	4-EtO-Ph	H	Me
2-188	H	NHPiv	4-EtO-Ph	H	Me
2-189	H	NH(MeOCO)	4-EtO-Ph	H	Me
2-190	H	NH(EtOCO)	4-EtO-Ph	H	Me
2-191	H	NH(BzOCO)	4-EtO-Ph	H	Me
2-192	H	NH($AcOCH_2$)	4-EtO-Ph	H	Me
2-193	H	NH($PmOCH_2$)	4-EtO-Ph	H	Me
2-194	H	NH($MeOCOOCH_2$)	4-EtO-Ph	H	Me
2-195	H	NH($EtOCOOCH_2$)	4-EtO-Ph	H	Me
2-196	H	NH[(5-Me-2-oxo-1,3-dioxolen-4-yl) CH_2]	4-EtO-Ph	H	Me
2-197	H	NH[(5-Ph-2-oxo-1,3-dioxolen-4-yl) CH_2]	4-EtO-Ph	H	Me
2-198	H	NHFor	3,4-diMe-Ph	H	Me
2-199	H	NHPrn	3,4-diMe-Ph	H	Me
2-200	H	NHByr	3,4-diMe-Ph	H	Me
2-201	H	NHiByr	3,4-diMe-Ph	H	Me
2-202	H	NHVal	3,4-diMe-Ph	H	Me
2-203	H	NHiVal	3,4-diMe-Ph	H	Me
2-204	H	NHPiv	3,4-diMe-Ph	H	Me
2-205	H	NH(MeOCO)	3,4-diMe-Ph	H	Me
2-206	H	NH(EtOCO)	3,4-diMe-Ph	H	Me
2-207	H	NH(BzOCO)	3,4-diMe-Ph	H	Me

Table 2 (continued)

Cpd. No.	R	R^1	R^2	R^3	R^4
2-208	H	NH($AcOCH_2$)	3,4-diMe-Ph	H	Me
2-209	H	NH($PmOCH_2$)	3,4-diMe-Ph	H	Me
2-210	H	NH($MeOCOOCH_2$)	3,4-diMe-Ph	H	Me
2-211	H	NH($EtOCOOCH_2$)	3,4-diMe-Ph	H	Me
2-212	H	NH[(5-Me-2-oxo-1,3-dioxolen-4-yl) CH_2]	3,4-diMe-Ph	H	Me
2-213	H	NH[(5-Ph-2-oxo-1,3-dioxolen-4-yl) CH_2]	3,4-diMe-Ph	H	Me

[0055] Of the compounds listed above, preferred compounds are:

1) 3-methyl-2-(4-methylphenyl)-1-(4-sulphamoylphenyl)pyrrole,

2) 4-methyl-2-(4-methylphenyl)-1-(4-sulphamoylphenyl)pyrrole,

3) 1-(4-fluorophenyl)-2-(4-sulphamoylphenyl)pyrrole,

4) 1-(4-fluorophenyl)-4-methyl-2-(4-sulphamoylphenyl)pyrrole,

5) 5-fluoro-1-(4-fluorophenyl)-2-(4-methylsulphonylphenyl)pyrrole,

6) 2-(4-methoxyphenyl)-4-methyl-1-(4-sulphamoylphenyl)pyrrole,

7) 1-(4-methoxyphenyl)-4-methyl-2-(4-sulphamoylphenyl)pyrrole,

8) 4-ethyl-2-(4-methoxyphenyl)-1-(4-sulphamoylphenyl)pyrrole,

9) 2-(4-chlorophenyl)-4-methyl-1-(4-sulphamoylphenyl)pyrrole,

10) 4-methyl-2-(4-methylthiophenyl)1-(4-sulphamoylphenyl)pyrrole,

11) 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulphamoylphenyl)pyrrole,

12) 2-(4-methoxy-3-methylphenyl)-4-methyl-1-(4-sulphamoylphenyl)pyrrole,

13) 2-(3-fluoro-4-methoxyphenyl)-4-methyl-1-(4-sulphamoylphenyl)pyrrole,

14) 4-methyl-2-phenyl-1-(4-sulphamoylphenyl)pyrrole,

15) 2-(3,4-dimethylphenyl)-4-methyl-1-(4-sulphamoylphenyl)pyrrole,

16) 2-(3-chloro-4-methoxyphenyl)-4-methyl-1-(4-sulphamoylphenyl)pyrrole,

17) 4-methyl-1-(4-methylthiophenyl)-2-(4-sulphamoylphenyl)pyrrole,

18) 5-chloro-1-(4-methoxyphenyl)-2-(4-sulphamoylphenyl)pyrrole,

19) 1-(3,4-dimethylphenyl)-4-methyl-2-(4-sulphamoylphenyl)pyrrole,

20) 5-chloro-1-(4-ethoxyphenyl)-2-(4-sulphamoylphenyl)pyrrole,

21) 5-chloro-1-(4-methylthiophenyl)-2-(4-sulphamoylphenyl)pyrrole,

22) 1-(4-ethylthiophenyl)-4-methyl-2-(4-sulphamoylphenyl)pyrrole,

23) 2-(3,5-dimethylphenyl)-4-methyl-1-(4-sulphamoylphenyl)pyrrole,

24) 1-(4-mercaptophenyl)-4-methyl-2-(4-sulphamoylphenyl)pyrrole,

25) 1-(4-acetylthiophenyl)-4-methyl-2-(4-sulphamoylphenyl)pyrrole,

26) 1-(4-acetylaminosulphonylphenyl)-4-methyl-2-(4-methoxyphenyl)pyrrole, and

27) 1-(4-acetylaminosulphonylphenyl)-4-methyl-2-(3,4-dimethylphenyl)pyrrole.

[0056] Of these, more preferred compounds are:

2) 4-methyl-2-(4-methylphenyl)-1-(4-sulphamoylphenyl)pyrrole,

6) 2-(4-methoxyphenyl)-4-methyl-1-(4-sulphamoylphenyl)pyrrole,

9) 2-(4-chlorophenyl)-4-methyl-1-(4-sulphamoylphenyl)pyrrole,

10) 4-methyl-2-(4-methylthiophenyl)-1-(4-sulphamoylphenyl)pyrrole,

11) 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulphamoylphenyl)pyrrole,

12) 2-(4-methoxy-3-methylphenyl)-4-methyl-1-(4-sulphamoylphenyl)pyrrole,

13) 2-(3-fluoro-4-methoxyphenyl)-4-methyl-1-(4-sulphamoylphenyl)pyrrole,

15) 2-(3,4-dimethylphenyl)-4-methyl-1-(4-sulphamoylphenyl)pyrrole,

17) 4-methyl-1-(4-methylthiophenyl)-2-(4-sulphamoylphenyl)pyrrole,

26) 1-(4-acetylaminosulphonylphenyl)-4-methyl-2-(4-methoxyphenyl)pyrrole, and

27) 1-(4-acetylaminosulphonylphenyl)-4-methyl-2-(3,4-dimethylphenyl)pyrrole.

[0057] Of these, the most preferred compounds are:

11) 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulphamoylphenyl)pyrrole,

15) 2-(3,4-dimethylphenyl)-4-methyl-1-(4-sulphamoylphenyl)pyrrole,

17) 4-methyl-1-(4-methylthiophenyl)-2-(4-sulphamoylphenyl)pyrrole,

26) 1-(4-acetylaminosulphonylphenyl)-4-methyl-2-(4-methoxyphenyl)pyrrole, and

27) 1-(4-acetylaminosulphonylphenyl)-4-methyl-2-(3,4-dimethylphenyl)pyrrole.

[0058] The compounds of formula (I), compounds of formula (II) and pharmaceutically acceptable salts of these compounds are known compounds and a method of preparing these compounds is disclosed in European Patent Publication EP-799823A.

[0059] The chemical names of the compounds of formulae (III) to (XIV), respectively, are:

(III): 3-(3,4-difluorophenyl)-4-(4-methanesulphonylphenyl)-5H-furan-2-one,

(IV): 4-(5-p-tolyl-3-trifluoromethyl-1H-pyrazol-1-yl)benzenesulphonamide,

(V): N-[6-(2,4-difluorophenylthio)-1-oxoindan-5-yl]methanesulphonamide,

(VI): 4-hydroxy-2-methyl-N-(5-methylthiazol-2-yl)-2H-1,2-benzothiazine-3-carboxamide-1,1-dioxide,

(VII): N-(4-Nitro-2-phenoxyphenyl)methanesulphonamide,

(VIII): 4-(4-cyclohexyl-2-methyloxazol-5-yl)-2-fluorobenzenesulphonamide,

(IX): N-(3-formylamino-4-oxo-6-phenoxy-4H-1-benzopyran-7-yl)methane-sulphonamide,

(X): (E)-2-ethyl-5-(3,5-di-t-butyl-4-hydroxy)benzylidene-1,2-isothiazolidine-1,1-dioxide,

(XI): 1-(4-methanesulphonylphenyl)-2-(4-fluorophenyl)cyclopentene,

(XII): 3-phenyl-4-(4-methanesulphonylphenyl)-5H-furan-2-one, and

(XIII): 2-(3,5-difluorophenyl)-3-(4-methanesulphonylphenyl)-2-cyclopenten-1-one.

(XIV): 4-[5-methyl-3-phenylisoxazol-4-yl)benzenesulphonamide.

[0060] These compounds are disclosed in International publication number WO95/00501, J. Med. Chem., 40, 1347 (1997), International publication number WO94/13635, Pharmacology, 55, 44 (1997), Prostaglandins, 47, 55 (1994), Japanese publication number Hei 9-52882, Jpn. J. Pharmacol., 67, 305 (1995), Inflamm. Res., 47, Suppl. 3, S257 (1997), J. Med. Chem., 38, 4570 (1995), EP 863 134, US 5 474 995 or WO 98/06708.

[0061] Since the compounds of the present invention have excellent activity for the prevention or inhibition of cachexia and very little toxicity, they are useful as preventive and therapeutic agents for cachexia. They are also useful for the treatment of tumour-related disorders, and can be used to inhibit the growth and/or metastasis of tumours.

[0062] Moreover, if desired, one or more of the compounds of the present invention [i.e. the compounds of formulae (I) to (XIV), inclusive] may be used in association with one or more other agents for the prevention or inhibition of tumour growth, and the compounds of the present invention and other agents may be administered simultaneously, separately or sequentially.

[0063] The other anti-tumour agent is preferably selected from 5-fluorouracil, cisplatin, tamoxifen, paclitaxel, docetaxel and irinotecan. Especially in the case of simultaneous administration, the compound of formula (I) or (II) or a pharmaceutically acceptable salt thereof and the other anti-tumour agent may be contained in a single composition.

[0064] The composition of the present invention may be in any conventional form, depending on the route of administration. For example, for oral administration, it may be in the form of tablets, capsules, granules, powders or syrups. For non-oral administration it may be in the form of injections or suppositories. These formulations are prepared according to known methods and may include additives such as are well known in the art, for example excipients (e.g., organic excipients including sugar derivatives, such as lactose, sucrose, glucose, mannitol and sorbitol; starch derivatives, such as corn starch, potato starch, α-starch and dextrin; cellulose derivatives, such as crystalline cellulose; gum arabic; dextran; and Pullulan, inorganic excipients including silicate derivatives, such as light silicic acid anhydride, synthetic aluminium silicate, calcium silicate and magnesium metasilicate aluminate; phosphates, such as calcium hydrogenphosphate; carbonates, such as calcium carbonate; and sulphates, such as calcium sulphate), lubricants (e.g., stearic acid and metal salts thereof, including stearic acid, calcium stearate and magnesium stearate; talc; colloidal silica; waxes, such as beeswax and spermaceti; boric acid; adipic acid; sulphates, such as sodium sulphate; glycol; fumaric acid; sodium benzoate; DL-leucine; fatty acid sodium salts; lauryl sulphates, such as sodium lauryl sulphate and magnesium lauryl sulphate; silicic acids, such as silicic acid anhydride and silicic acid hydrate; and the above-mentioned starch derivatives), binders (e.g., hydroxypropyl cellulose, hydroxypropylmethyl cellulose, polyvinyl pyrrolidone, Macrogol and similar compounds to the above-mentioned excipients), disintegrating agents (e.g., cellulose derivatives, such as low-substituted hydroxypropyl cellulose, carboxymethyl cellulose, calcium carboxymethyl cellulose, internally bridged sodium carboxymethyl cellulose; chemically modified starch-celluloses, such as carboxymethyl starch, sodium carboxymethyl starch and bridged polyvinyl pyrrolidone), stabilizers (e.g., paraoxybenzoates, such as methylparaben and propylparaben; alcohols, such as chlorobutanol, benzyl alcohol and phenylethyl alcohol; benzalkonium chloride; phenols, such as phenol and cresol; thimerosal; dehydroacetic acid; and sorbic acid), corrigents (e.g., sweeteners, vinegars and perfumes) and diluents.

[0065] The dose varies, depending on many factors, including the condition and age of the patients, the severity and nature of the disorder and the route of administration. For example, in the case of oral administration, it is desirable to administer 0.01 mg/kg (preferably 0.1 mg/kg) as a lower limit and 50 mg/kg (preferably 10 mg/kg) as an upper limit for

an adult per day, in a single dose or in divided doses, depending on the symptoms. In the case of intravenous administration, it is desirable to administer 0.001 mg/kg (preferably 0.01 mg/kg) as a lower limit and 10 mg/kg (preferably 5 mg/kg) as an upper limit for an adult, in a single dose or in divided doses, depending on the symptoms.

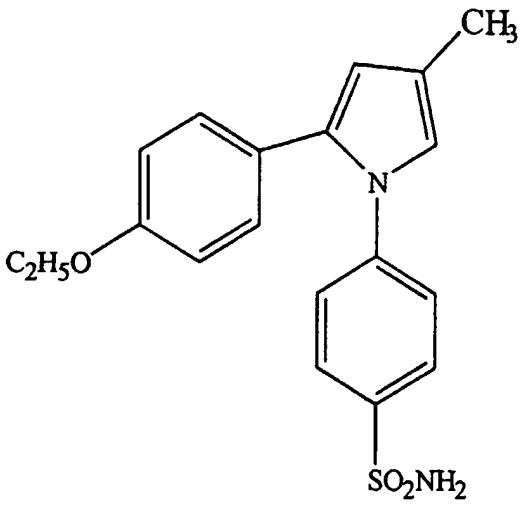
[0066] The present invention is further illustrated by the following non-limiting Examples and Formulation examples.

EXAMPLE 1

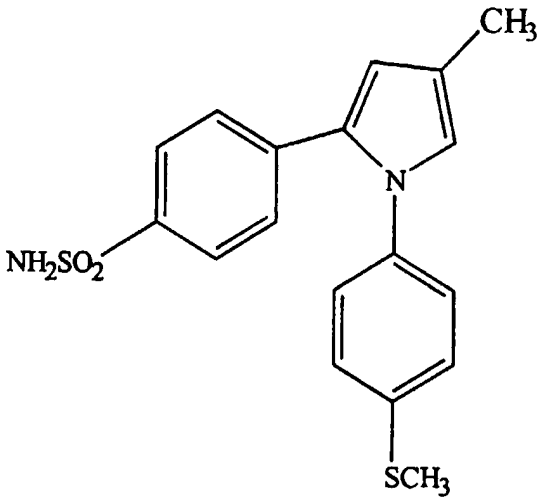
Test of Anticachexia Effects in Mice bearing Mouse Colon Cancer Colon 26 Cells

[0067] The test animals were CDFI mice (females, 8 weeks old). They were employed in groups of 10 for each test. 1x 10^6 mouse colon cancer Colon 26 cells were transplanted subcutaneously into each animal.

[0068] The test compounds were Compounds No. 1-94 and 2-78 as shown above in Tables 1 and 2, respectively, and having the following formulae:



Compound No. 2-78



Compound No. 1-94

[0069] Each test compound was suspended in sterilized distilled water containing 0.5% w/v carboxymethyl cellulose (CMC) and administered orally once per day starting on the day of the tumour cell transplantation.

[0070] Each test animal was weighed immediately after tumour cell transplantation, and the weight (A g) was recorded. Each animal was then weighed on day 19 after tumour cell transplantation, and the weight (B g) was recorded. The weight gain on day 19 after tumour cell transplantation was calculated as B-A = Δg_t for the test animals. The experiment was repeated with two control groups: the first control group (control group 1) was transplanted with the tumour cells but were not treated with any test compound, and the weight gain is reported as Δg_{c1} ; the second control group (control group 2) were not transplanted with the tumour cells and were not treated with any test compound, and the weight gain is reported as Δg_{c2}. The body weight recovery rate was determined according to the following formula based on the weight gain on day 19 after tumour cell transplantation, and this value was used as an indicator of the anticachexia effect.

$$\text{Body weight recovery rate (\%)} = (\Delta g_t - \Delta g_{c1})/(\Delta g_{c2} - \Delta g_{c1}) \times 100$$

[0071] The results are shown in Table 3 below.

Table 3

Administered Compound	Dose (mg/kg)	Weight Gain (Δg)	Body Weight Recovery Rate (%)
Compound 2-78	10	2.6	88
Compound 2-78	3	2.5	85
Compound 2-78	1	2.5	85
Compound 1-94	10	3.1	98
Compound 1-94	3	2.7	89
Compound 1-94	1	2.2	78
control group 1	-	-1.4	0
control group 2	-	3.2	100

[0072] It is clear from the above results that these compounds inhibited mouse tumour cachexia and reduced weight loss.

EXAMPLE 2

Test of Anticachexia Effects in Mice bearing Mouse Colon Cancer Colon 26 Cells

[0073] The procedure described in Example 1 was repeated, but using the compound of formula (III) as the test compound, and comparing the weight gain (Δg_t) of the test group of animals to which the compound of formula (III) had been administered with a control group (Δg_c) into which the tumour cells had been transplanted but to which no anti-tumour compound had been administered. The test animals were female CDF1 mice, 16 weeks old. Also, the weight gain was measured 22 days after tumour transplantation. The average body weight of each group of animals immediately after tumour transplantation was 25 to 26 g. The results are shown in Table 4.

Table 4

Compound	Dose (mg/kg)	Average Weight Gain (Δg)
Compound (III)	10	0.9
Compound (III)	3	0.3
Compound (III)	1	0.0
None (Control group)	-	-4.2

[0074] It is clear from the above results that the compound of formula (III) inhibited mouse tumour cachexia and reduced weight loss.

EXAMPLE 3

Test of Anticachexia Effects in Mice bearing Mouse Colon Cancer Colon 26 Cells

[0075] The procedure described in Example 2 was repeated, but using the compound of formula (IV) as the test compound, and comparing the weight gain (Δg_t) of the test group of animals to which the compound of formula (IV) had been administered with a control group (Δg_c) into which the tumour cells had been transplanted but to which no anti-tumour compound had been administered. The test animals were female CDF1 mice, 7 weeks old. Also, the weight gain was measured 15 days after tumour transplantation. The average body weight of each group of animals immediately after tumour transplantation was 20 to 21 g. The results are shown in Table 5.

Table 5

Compound	Dose (mg/kg)	Average Weight Gain (Δg)
Compound (IV)	10	-0.6

Table 5 (continued)

Compound	Dose (mg/kg)	Average Weight Gain (Δg)
Compound (IV)	3	-1.3
Compound (IV)	1	-1.2
None (Control group)	-	-3.4

[0076] It is clear from the above results that the compound of formula (IV) inhibited mouse tumour cachexia and reduced weight loss.

EXAMPLE 4

Test of Anticachexia Effects in Mice bearing Mouse Colon Cancer Colon 26 Cells

[0077] Test compounds [the compounds of formula (V), (VI), (VII), (VIII), (IX), (X), (XI), (XII), (XIII) and (XIV)] are administered in the same manner as described in Example 2. These compounds inhibit mouse tumour cachexia and recover loss of average of body weight.

EXAMPLE 5

Life-prolonging Activity Test

[0078] Observation of the mice used in Example 1 above was continued. The life-prolonging index was determined, based on the number of days each mouse survived, and this value was then used as an indicator of the life-prolonging effects of the test compounds.

[0079] It should be noted that, in the case of the group of mice treated with a test compound, oral administration of the respective compound once daily was continued on day 20 after tumour cell transplantation and beyond as well.

$$\text{Life-prolonging index (\%)} = (S_t/S_c - 1) \times 100$$

S_t: Median value of survival time (days) of the group of mice treated with a test compound

S_c: Median value of survival time (days) of the control group which were not transplanted with tumour cells.

[0080] The results are shown in Table 6.

Table 6

Compound Name	Dose (mg/kg)	Survival Period (median: days)	Life-prolonging Index (%)
Compound 2-78	10	48.5	73
Compound 2-78	3	50.5	80
Compound 2-78	1	45.0	61
Compound 1-94	10	45.0	61
Compound 1-94	3	35.0	25
Compound 1-94	1	48.5	73
None	-	28.0	0

[0081] As is clear from Table 6, the compounds of the present invention exhibited a prominent life-prolonging effect.

EXAMPLE 6

Life-prolonging Activity Test

[0082] The experiment reported in Example 5 was repeated with the animals used in Example 2. In the case of the group of mice treated with a test compound, oral administration of the respective compound once daily was continued on day 23 after tumour cell transplantation and beyond as well. The results are shown in Table 7.

Table 7

Compound Name	Dose (mg/kg)	Survival Period (median: days)	Life-prolonging Index (%)
Compound (III)	10	43.5	91
Compound (III)	3	37.5	63
Compound (III)	1	40.5	76
None	-	23.0	-

EXAMPLE 7

Life-prolonging Activity Test

[0083] The experiment reported in Example 5 is repeated with the animals used in Examples 3 and 4. The compounds of formulae (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI), (XII), (XIII) and (XIV) all inhibit mouse tumour cachexia and exhibit pronounced life-prolongation.

EXAMPLE 8

Test of concomitant use of anti-tumour agent

[0084] Mouse colon cancer cells are transplanted into CDF1 mice in the same manner as Example 1 followed by administration of the test compounds [Compound Nos. 2-78 and 1-94, and the compounds of formulae (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI), (XII), (XIII) and (XIV)] and an anti-tumour agent (5-fluorouracil or cisplatin).

[0085] The concomitant use of one of the compounds of the present invention and an anti-tumour agent remarkably inhibits tumour growth and cachexia, to afford a pronounced life-prolonging effect.

EXAMPLE 9

Inhibitory effect on lung metastasis of mouse malignant melanoma B16-BL6 cells

[0086] Groups of mice, each group containing ten C57BL/6 mice (female, age: 8 weeks) were transplanted intravenously into the tail vein with 3×10^4 of mouse malignant melanoma B16-BL6 cells.

[0087] The mice were, when necessary, administered intravenously into the tail vein with a bacterial lipopolysaccharide (LPS) in an amount of 3 μg each within one hour before transplantation of the melanoma cells so as to accelerate lung metastasis of the melanoma [M. J. Anasagasti et al., J. Natl. Cancer Research, 89, 645-651 (1997).]

[0088] As test compounds, Compound No. 2-118, a compound of formula (IV), a compound of formula (V) and indomethacin were employed, and each was suspended in sterilized distilled water containing 0.5 % w/v of carboxymethyl cellulose (CMC), and the suspensions were orally administered at a dose of 1 mg/kg per day for five days starting from the day of the melanoma cell transplantation.

[0089] Compound No. 2-118 is 2-(3,4-dimethylphenyl)-4-methyl-1-(4-sulphamoylphenyl)pyrrole.

[0090] Inhibitory activities on lung metastasis of the melanoma cells were evaluated in terms of the lung metastasis inhibitory rate (LMI %) by counting the number of metastatic colonies in the lung on the 10th day after intravenous transplantation of the mouse malignant melanoma B16-BL6 cells at the tail.

$$LMI\ (\%) = (1-N_t/N_c) \times 100$$

N_t: Numbers of lung metastatic colonies on the 10th day in groups administered with the test compounds; and

N_c: Numbers of lung metastatic colonies on the 10th day in control groups which were not administered with the test compounds.

[0091] The results are shown in Table 8.

Table 8

Test compound	LPS administration	Dose (mg/kg)	LMI (%)
Compound 2-118	No	1	64
Compound 2-118	Yes	1	34
Compound (IV)	Yes	1	9
Compound (V)	Yes	1	1
Indomethacin	Yes	1	-1

[0092] It is clear from Table 8 that the present composition was successful in inhibiting metastasis of the mouse malignant melanoma B16-BL6 cells to the lung whether or not lung metastasis was accelerated by the LPS administration (induction of inflammation reaction).

[0093] In particular, the present composition showed a marked inhibition of lung metastasis, while the compound of formula (IV) and the compound of formula (V), which are COX-2-selective inhibitors, and indomethacin, which is a typical NSAID, had no such inhibitory activity under the lung metastasis accelerating conditions caused by inducing inflammatory reaction (as reflecting acceleration of metastasis of tumour in a surgical operation of resecting a tumour).

EXAMPLE 10

Anti-tumour Effect Against Mouse Sarcoma S-180 Cells

[0094] 1×10^6 mouse sarcoma S-180 cells were transplanted subcutaneously in Balb/c nude mice (females, 8 weeks old) in groups of 10 each.

[0095] The test compound, Compound No. 2-118, was suspended in sterilized distilled water containing 0.5% w/v carboxymethyl cellulose (CMC) and administered orally once per day for 5 days starting on the day the tumour cells were transplanted.

[0096] Anti-tumour activity was assessed according to the following equation to determine the tumour growth inhibitory rate (GI%) on day 7 after the transplantation.

$$GI\ (\%) = (1 - V_t / V_c) \times 100$$

V_t: Mean tumour volume on day 7 in a group administered test compound (*)

V_c: Mean tumour volume on day 7 in an untreated control group (*)

*: Tumour volume is defined as 1/2 x [tumour long axis] x [tumour short axis]^2

[0097] The results are shown in Table 9.

Table 9

Test Compound	Dose (mg/kg)	GI (%)
Compound 2-118	1	54

[0098] It is clear from Table 9 that the composition of the present application inhibited the growth of mouse tumour cells.

EXAMPLE 11

Anti-tumour Effect Against Human Colon Canc r KM12-HX Cells

[0099] Human colon cancer KM12-HX cells were orthotopically transplanted into the cecum of nude mice according to the method of Fu *et al.* [X. Fu *et al.*, Anticancer Res., 12 (1992)] using Balb/c nude mice (females, 7 weeks old) in groups of 10 each. Specifically, an incision was made into the left lower abdominal region of each mouse under Abacin anesthesia, after which a thin section of tumour measuring 5 mm on a side was sutured to the cecum using absorbable surgical sutures to perform orthotopic transplant. The incision was sutured using absorbable surgical sutures and the mice were warmed and promptly awakened from anesthesia.

[0100] The test compound was suspended in sterilized distilled water containing 0.5% w/v carboxymethyl cellulose (CMC) and administered orally in a total of 9 doses consisting of one dose per day from days 3 to 7 after the tumour cell transplantation and from days 10 to 13 after the transplantation.

[0101] Anti-tumour activity was assessed according to the following equation to determine the tumour weight inhibitory rate (GI%) on day 14 after the transplantation.

$$GI\ (\%) = (1 - V_t'/V_c') \times 100$$

V_t': Mean tumour weight on day 14 in the group administered the test compound

V_c': Mean tumour weight on day 14 in an untreated control group

[0102] The results are shown in Table 10.

Table 10

Test Compound	Dose (mg/kg)	GI(%)
Compound 2-118	0.3	12
Compound 2-118	1	35
Compound 2-118	3	45
Compound 2-118	10	59

[0103] It is clear from Table 10 that the composition of the present invention inhibited the growth of human colon cancer cells at the orthotopic transplantation site.

[0104] Preparation of pharmaceutical formulations containing the compounds of the present invention is further illustrated by the following non-limiting Formulation Examples.

FORMULATION EXAMPLE 1

Capsules

[0105] A mixture of a compound of the present invention, such as the compound of formula (III), Compound No. 1-94, 2-78 or 2-118, is prepared in a digestive oily substance, such as soybean oil, cottonseed oil or olive oil, and filled into gelatin with a positive replacement pump to obtain soft capsules containing 100 mg of active ingredient. The resulting capsules are then washed and dried.

FORMULATION EXAMPLE 2

Tablets

[0106] Tablets are manufactured in accordance with conventional methods using 100 mg of a compound of the present invention, such as the compound of formula (III), Compound No. 1-94, 2-78 or 2-118, 0.2 mg of colloidal silicon dioxide, 5 mg of magnesium stearate, 275 mg of microcrystalline cellulose, 11 mg of starch and 98.8 mg of lactose.

[0107] In this case, the tablets can be coated with a preparation coating if desired.

FORMULATION EXAMPLE 3

Infections

[0108] 1.5% by weight of a compound of the present invention, such as the compound of formula (III), Compound No. 1-94, 2-78 or 2-118, is stirred in 10% by volume of propylene glycol, and is then adjusted to a constant volume by the addition of water for injection, after which it was sterilized to prepare injections.

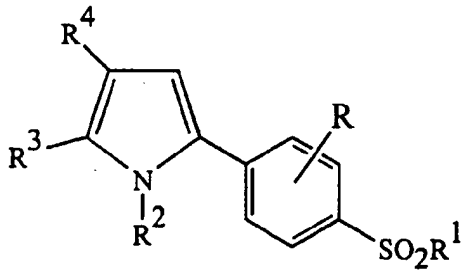
FORMULATION EXAMPLE 4

Suspensions

[0109] A suspension is produced so as to contain 100 mg of a compound of the present invention, such as the compound of formula (III), Compound No. 1-94, 2-78 or 2-118, which is ground into a fine powder, 100 mg of sodium carboxymethyl cellulose, 5 mg of sodium benzoate, 1.0 g of sorbitol solution (Japanese Pharmacopoeia) and 0.025 ml of vanillin in 5 ml of the suspension.

Claims

1. The use of a compound of formula (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI), (XII), (XIII) or (XIV):



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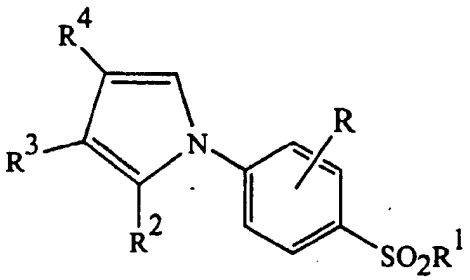

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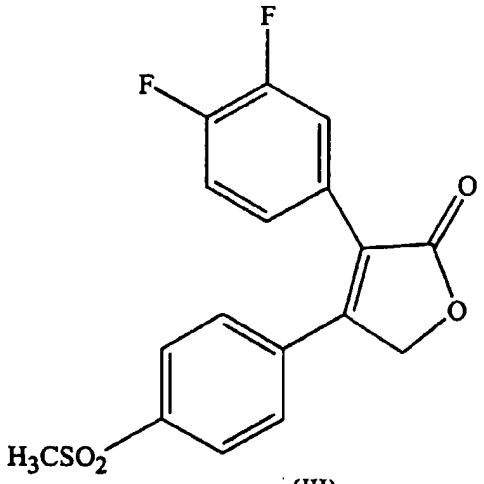

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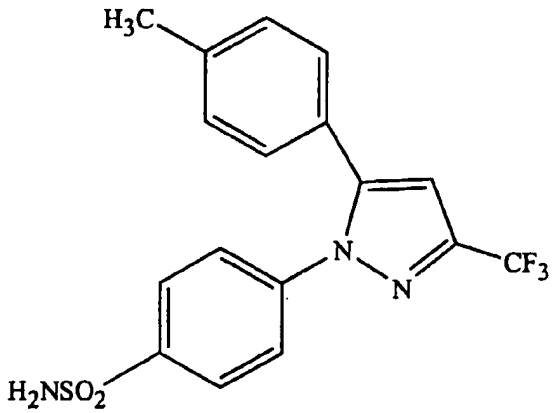

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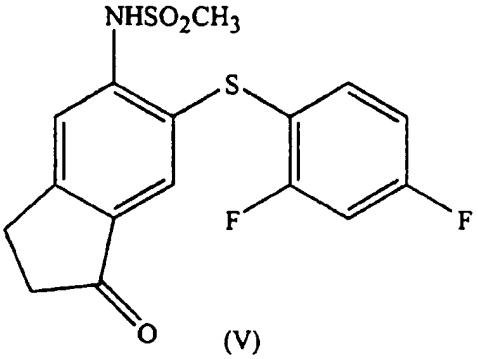

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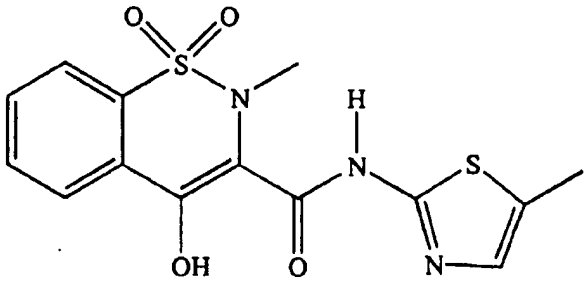

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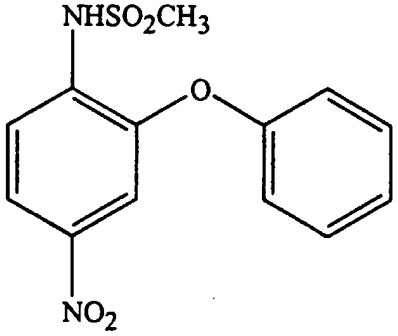

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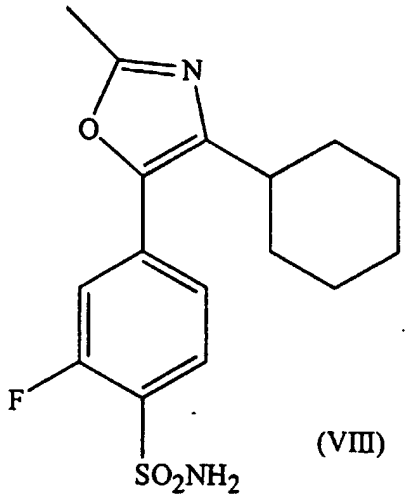

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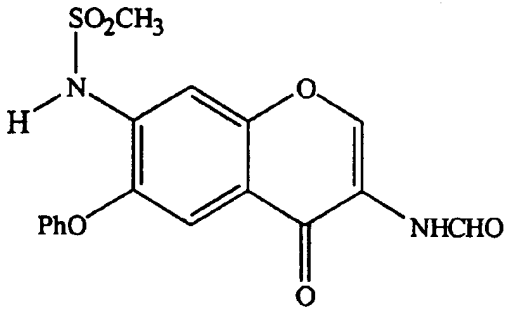

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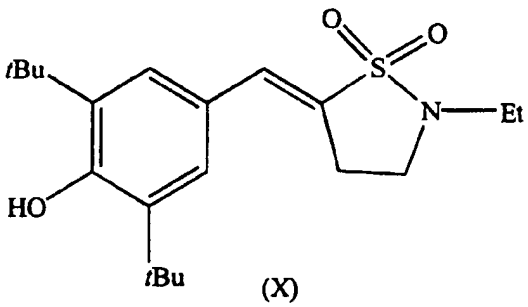

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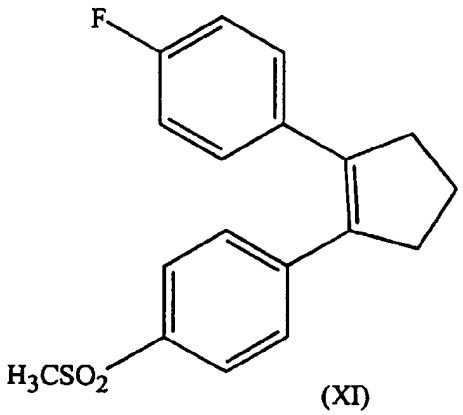

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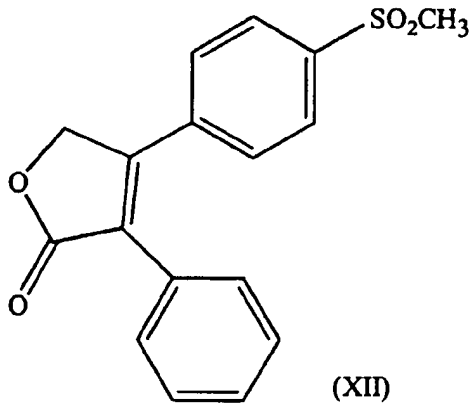

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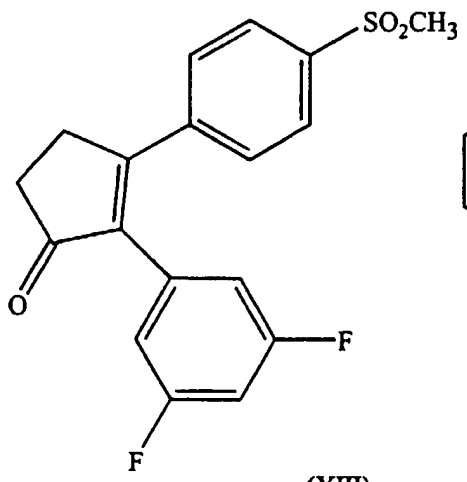

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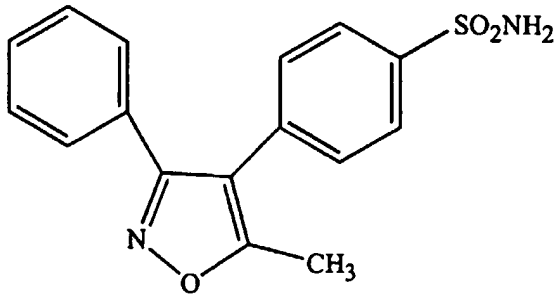


(XIV)

in which:

R represents a hydrogen atom, a halogen atom or a lower alkyl group;

R^1 represents a lower alkyl group, an amino group or a group of formula $-NHR^a$ (in which R^a represents a group which may be eliminated *in vivo);*

R^2 represents a phenyl group or a phenyl group substituted by at least one of substituents α or substituents β, defined below;

R^3 represents a hydrogen atom, a halogen atom, a lower alkyl group or a lower alkyl group substituted by at least one of substituents α;

R^4 represents a hydrogen atom, a lower alkyl group, a lower alkyl group substituted by at least one of substituents α, a cycloalkyl group, an aryl group as defined below, or an aralkyl group as defined below;

said aryl group is a carbocyclic aromatic hydrocarbon group having from 6 to 14 carbon atoms in one or more aromatic rings or such a group which is fused to a cycloalkyl group having from 3 to 10 carbon atoms, and the

group is unsubstituted or it is substituted by at least one of substituents α or substituents β;

said aralkyl group is a lower alkyl group which is substituted by one or more of the aryl groups defined above;

*t*Bu represents a t-butyl group;

Et represents an ethyl group; and

Ph represents a phenyl group;

said substituents α are selected from hydroxy groups, halogen atoms, lower alkoxy groups and lower alkylthio groups; and

said substituents β are selected from lower alkyl groups, alkanoyloxy groups, mercapto groups, alkanoylthio groups, lower alkylsulphinyl groups, lower alkyl groups substituted by at least one of substituents α, cycloalkyloxy groups, lower haloalkoxy groups and lower alkylenedioxy groups;

or a pharmaceutically acceptable salt thereof
for the manufacture of a medicament for the treatment or prevention of cachexia in a mammal.

2. A use according to Claim 1, in which said active compound is a compound of formula (I) or (II).

3. A use according to Claim 2, in which R represents a hydrogen atom, a fluorine atom, a chlorine atom or a methyl group.

4. A use according to Claim 3, in which R represents a hydrogen atom.

5. A use according to any one of Claims 2 to 4, in which R^1 represents a methyl group, an amino group or an acetylamino group.

6. A use according to Claim 5, in which R^1 represents an amino group or an acetylamino group.

7. A use according to any one of Claims 2 to 6, in which R^2 represents a phenyl group or a phenyl group substituted with at least one of substituents α^1 or substituents β^1.

substituents α^1 are selected from halogen atoms, lower alkoxy groups and lower alkylthio groups; and

substituents β^1 are selected from lower alkyl groups, mercapto groups, alkanoylthio groups, lower alkyl groups substituted with at least one of substituents α^1, lower haloalkoxy groups and lower alkylenedioxy groups.

8. A use according to Claim 7, in which R^2 represents a phenyl group or a phenyl group substituted with at least one of substituents α^1 and substituents β^2.

substituents α^1 are selected from halogen atoms, lower alkoxy groups and lower alkylthio groups.

substituents β^2 are selected from lower alkyl groups, mercapto groups, alkanoylthio groups, lower alkyl groups substituted with a halogen atom, lower haloalkoxy groups and lower alkylenedioxy groups.

9. A use according to any one of Claims 2 to 8, in which R^3 represents a hydrogen atom, a halogen atom, a lower alkyl group or a lower alkyl group substituted with at least one of substituents α^1;
substituents α^1 are selected from halogen atoms, lower alkoxy groups and lower alkylthio groups.

10. A use according to Claim 9, in which R^3 represents a hydrogen atom, a halogen atom, a lower alkyl group or a lower alkyl group substituted with a halogen atom.

11. A use according to any one of Claims 2 to 10, in which R^4 represents a hydrogen atom, a lower alkyl group, a lower alkyl group substituted with at least one of substituents α, a cycloalkyl group, an aryl group, an aryl group substituted with at least one of substituents α^1 or substituents β^3, an aralkyl group or an aralkyl group substituted

with at least one of substituents α^1 or substituents β^3;

substituents α^1 are selected from halogen atoms, lower alkoxy groups and lower alkylthio groups; and

substituents β^3 are selected from lower alkyl groups, lower alkyl groups substituted with at least one of substituents a and cycloalkyloxy groups.

12. A use according to Claim 11, in which R^4 represents a hydrogen atom, a lower alkyl group, a lower alkyl group substituted with at least one of substituents α^2, a cycloalkyl group, an aryl group, an aryl group substituted with at least one of substituents α^2 or substituents β^4, an aralkyl group or an aralkyl group substituted with at least one of substituents α^2 or substituents β^4;

substituents α^2 are selected from hydroxy groups, halogen atoms and lower alkoxy groups; and

substituents β^4 are selected from lower alkyl groups, lower alkyl groups substituted with halogen atom and cycloalkyloxy groups.

13. A use according to Claim 2, in which said active compound is:

3-methyl-2-(4-methylphenyl)-1-(4-sulphamoylphenyl)pyrrole,

4-methyl-2-(4-methylphenyl)-1-(4-sulphamoylphenyl)pyrrole,

1-(4-fluorophenyl)-2-(4-sulphamoylphenyl)pyrrole,

1-(4-fluorophenyl)-4-methyl-2-(4-sulphamoylphenyl)pyrrole,

5-fluoro-1-(4-fluorophenyl)-2-(4-methylsulphonylphenyl)pyrrole,

2-(4-methoxyphenyl)-4-methyl-1-(4-sulphamoylphenyl)pyrrole,

1-(4-methoxyphenyl)-4-methyl-2-(4-sulphamoylphenyl)pyrrole,

4-ethyl-2-(4-methoxyphenyl)-1-(4-sulphamoylphenyl)pyrrole,

2-(4-chlorophenyl)-4-methyl-1-(4-sulphamoylphenyl)pyrrole,

4-methyl-2-(4-methylthiophenyl)-1-(4-sulphamoylphenyl)pyrrole,

2-(4-ethoxyphenyl)-4-methyl-1-(4-sulphamoylphenyl)pyrrole,

2-(4-methoxy-3-methylphenyl)-4-methyl-1-(4-sulphamoylphenyl)pyrrole,

2-(3-fluoro-4-methoxyphenyl)-4-methyl-1-(4-sulphamoylphenyl)pyrrole,

4-methyl-2-phenyl-1-(4-sulphamoylphenyl)pyrrole,

2-(3,4-dimethylphenyl)-4-methyl-1-(4-sulphamoylphenyl)pyrrole,

2-(3-chloro-4-methoxyphenyl)-4-methyl-1-(4-sulphamoylphenyl)pyrrole,

4-methyl-1-(4-methylthiophenyl)-2-(4-sulphamoylphenyl)pyrrole,

5-chloro-1-(4-methoxyphenyl)-2-(4-sulphamoylphenyl)pyrrole,

1-(3,4-dimethylphenyl)-4-methyl-2-(4-sulphamoylphenyl)pyrrole,

5-chloro-1-(4-ethoxyphenyl)-2-(4-sulphamoylphenyl)pyrrole,

5-chloro-1-(4-methylthiophenyl)-2-(4-sulphamoylphenyl)pyrrole,

1-(4-ethylthiophenyl)-4-methyl-2-(4-sulphamoylphenyl)pyrrole,

2-(3,5-dimethylphenyl)-4-methyl-1-(4-sulphamoylphenyl)pyrrole,

1-(4-mercaptophenyl)-4-methyl-2-(4-sulphamoylphenyl)pyrrole,

1-(4-acetylthiophenyl)-4-methyl-2-(4-sulphamoylphenyl)pyrrole,

1-(4-acetylaminosulphonylphenyl)-4-methyl-2-(4-methoxyphenyl)pyrrole, or

1-(4-acetylaminosulphonylphenyl)-4-methyl-2-(3,4-dimethylphenyl)pyrrole,

or a pharmaceutically acceptable salt thereof.

14. A use according to Claim 2, in which said active compound is:

2-(4-chlorophenyl)-4-methyl-1-(4-sulphamoylphenyl)pyrrole,

2-(4-ethoxyphenyl)-4-methyl-1-(4-sulphamoylphenyl)pyrrole,

2-(3,4-dimethylphenyl)-4-methyl-1-(4-sulphamoylphenyl)pyrrole,

4-methyl-1-(4-methylthiophenyl)-2-(4-sulphamoylphenyl)pyrrole, or

1-(4-acetylaminosulphonylphenyl)-4-methyl-2-(3,4-dimethylphenyl)pyrrole,

or a pharmaceutically acceptable salt thereof.

15. A use according to Claim 1, in which said active compound is a compound of formulae (III), (IV), (V), (VI), (VII), (VIII), (IX), (X) or (XI).

16. A use according to Claim 15, in which said active compound is 3-(3,4-difluorophenyl)-4-(4-methanesulphonylphenyl)-5H-furan-2-one or a pharmaceutically acceptable salt thereof.

17. A use according to Claim 15, in which said active compound is 4-(5-p-tolyl-3-trifluoromethyl-1H-pyrazol-1-yl)benzenesulphonamide or a pharmaceutically acceptable salt thereof.

18. A use according to Claim 15, in which said active compound is N-[6-(2,4-difluorophenylthio)-1-oxoindan-5-yl]methanesulphonamide or a pharmaceutically acceptable salt thereof.

19. A use according to Claim 15, in which said active compound is 4-hydroxy-2-methyl-N-(5-methylthiazol-2-yl)-2H-1,2-benzothiazine-3-carboxamide-1,1-dioxide or a pharmaceutically acceptable salt thereof.

20. A use according to Claim 15, in which said active compound is N-(4-Nitro-2-phenoxyphenyl)methanesulphonamide or a pharmaceutically acceptable salt thereof.

21. A use according to Claim 15, in which said active compound is 4-(4-cyclohexyl-2-methyloxazol-5-yl)-2-fluorobenzenesulphonamide or a pharmaceutically acceptable salt thereof.

22. A use according to Claim 15, in which said active compound is N-(3-formylamino-4-oxo-6-phenoxy-4H-1-benzopyran-7-yl)methanesulphonamide or a pharmaceutically acceptable salt thereof.

23. A use according to Claim 15, in which said active compound is (E)-2-ethyl-5-(3,5-di-t-butyl-4-hydroxy)benzylidene-1,2-isothiazolidine-1,1-dioxide or a pharmaceutically acceptable salt thereof.

24. A use according to Claim 15, in which said active compound is 1-(4-methanesulphonylphenyl)-2-(4-fluorophenyl)

cyclopentene or a pharmaceutically acceptable salt thereof.

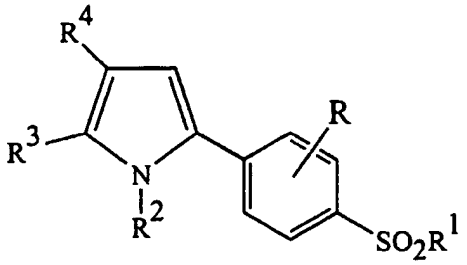
25. A use according to Claim 1, in which said active compound is a compound of formula (XII), (XIII) and (XIV).

26. A use according to Claim 25, in which said active compound is 3-phenyl-4-(4-methanesulphonylphenyl)-5H-furan-2-one or a pharmaceutically acceptable salt thereof.

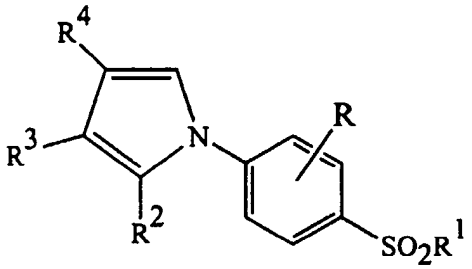
27. A use according to Claim 25, in which said active compound is 2-(3,5-difluorophenyl)-3-(4-methanesulphonylphenyl)-2-cyclopenten-1-one or a pharmaceutically acceptable salt thereof.

28. A use according to Claim 25, in which said active compound is 4-[5-methyl-3-phenylisoxazol-4-yl)benzenesulphonamide or a pharmaceutically acceptable salt thereof.

29. The use of a compound of formula (I) or (II):



(I)



(II)

in which

R represents a hydrogen atom, a halogen atom or a lower alkyl group;

R^1 represents a lower alkyl group, an amino group or a group of formula $-NHR^a$ (in which R^a represents a group which may be eliminated *in vivo*);

R^2 represents a phenyl group or a phenyl group substituted by at least one of substituents α or substituents β, defined below;

R^3 represents a hydrogen atom, a halogen atom, a lower alkyl group or a lower alkyl group substituted by at least one of substituents α;

R^4 represents a hydrogen atom, a lower alkyl group, a lower alkyl group substituted by at least one of substituents α, a cycloalkyl group, an aryl group a defined below, or an aralkyl group as defined below;

said aryl group is a carbocyclic aromatic hydrocarbon group having from 6 to 14 carbon atoms in one or more aromatic rings or such a group which is fused to a cycloalkyl group having from 3 to 10 carbon atoms, and the group is unsubstituted or it is substituted by at least one of substituents α or substituents β;

said aralkyl group is a lower alkyl group which is substituted by one or more of the aryl groups defined above;

said substituents α are selected from hydroxy groups, halogen atoms, lower alkoxy groups and lower alkylthio groups; and

said substituents β are selected from lower alkyl groups, alkanoyloxy groups, mercapto groups, alkanoylthio groups, lower alkylsulphinyl groups, lower alkyl groups substituted by at least one of substituents α, cycloalky-

loxy groups, lower haloalkoxy groups and lower alkylenedioxy groups;

or a pharmaceutically acceptable salts thereof
for the manufacture of a medicament for the treatment or prevention of tumour-related disorders in a mammal.

30. A use according to Claim 29, in which R represents a hydrogen atom, a fluorine atom, a chlorine atom or a methyl group.

31. A use according to Claim 30, in which R represents a hydrogen atom.

32. A use according to any one of Claims 29 to 31, in which R^1 represents a methyl group, an amino group or an acetylamino group.

33. A use according to Claim 32, in which R^1 represents an amino group or an acetylamino group.

34. A use according to any one of Claims 29 to 33, in which R^2 represents a phenyl group or a phenyl group substituted with at least one of substituents α^1 or substituents β^1;

substituents α^1 are selected from halogen atoms, lower alkoxy groups and lower alkylthio groups; and

substituents β^1 are selected from lower alkyl groups, mercapto groups, alkanoylthio groups, lower alkyl groups substituted with at least one of substituents α^1, lower haloalkoxy groups and lower alkylenedioxy groups.

35. A use according to Claim 34, in which R^2 represents a phenyl group or a phenyl group substituted with at least one of substituents α^1 or substituents β^2;

substituents α^1 are selected from halogen atoms, lower alkoxy groups and lower alkylthio groups.

substituents β^2 are selected from lower alkyl groups, mercapto groups, alkanoylthio groups, lower alkyl groups substituted with a halogen atom, lower haloalkoxy groups and lower alkylenedioxy groups.

36. A use according to any one of Claims 29 to 35, in which R^3 represents a hydrogen atom, a halogen atom, a lower alkyl group or a lower alkyl group substituted with at least one of substituents α^1;
substituents α^1 are selected from halogen atoms, lower alkoxy groups and lower alkylthio groups.

37. A use according to Claim 36, in which R^3 represents a hydrogen atom, a halogen atom, a lower alkyl group or a lower alkyl group substituted with a halogen atom.

38. A use according to any one of Claims 29 to 37, in which R^4 represents a hydrogen atom, a lower alkyl group, a lower alkyl group substituted with at least one of substituents α, a cycloalkyl group, an aryl group, an aryl group substituted with at least one of substituents α^1 or substituents β^3, an aralkyl group or an aralkyl group substituted with at least one of substituents α^1 or substituents β^3;

substituents α^1 are selected from halogen atoms, lower alkoxy groups and lower alkylthio groups; and

substituents β^3 are selected from lower alkyl groups, lower alkyl groups substituted with at least one of substituents α and cycloalkyloxy groups.

39. A use according to Claim 38, in which R^4 represents a hydrogen atom, a lower alkyl group, a lower alkyl group substituted with at least one of substituents α^2, a cycloalkyl group, an aryl group, an aryl group substituted with at least one of substituents α^2 or substituents β^4, an aralkyl group or an aralkyl group substituted with at least one of substituents α^2 or substituents β^4;

substituents α^2 are selected from hydroxy groups, halogen atoms and lower alkoxy groups; and

substituents β^4 are selected from lower alkyl groups, lower alkyl groups substituted with halogen atom and cycloalkyloxy groups.

40. A use according to Claim 29, in which said active compound is:

3-methyl-2-(4-methylphenyl)-1-(4-sulphamoylphenyl)pyrrole,

4-methyl-2-(4-methylphenyl)-1-(4-sulphamoylphenyl)pyrrole,

1-(4-fluorophenyl)-2-(4-sulphamoylphenyl)pyrrole,

1-(4-fluorophenyl)-4-methyl-2-(4-sulphamoylphenyl)pyrrole,

5-fluoro-1-(4-fluorophenyl)-2-(4-methylsulphonylphenyl)pyrrole,

2-(4-methoxyphenyl)-4-methyl-1-(4-sulphamoylphenyl)pyrrole,

1-(4-methoxyphenyl)-4-methyl-2-(4-sulphamoylphenyl)pyrrole,

4-ethyl-2-(4-methoxyphenyl)-1-(4-sulphamoylphenyl)pyrrole,

2-(4-chlorophenyl)-4-methyl-1-(4-sulphamoylphenyl)pyrrole,

4-methyl-2-(4-methylthiophenyl)-1-(4-sulphamoylphenyl)pyrrole,

2-(4-ethoxyphenyl)-4-methyl-1-(4-sulphamoylphenyl)pyrrole,

2-(4-methoxy-3-methylphenyl)-4-methyl-1-(4-sulphamoylphenyl)pyrrole,

2-(3-fluoro-4-methoxyphenyl)-4-methyl-1-(4-sulphamoylphenyl)pyrrole,

4-methyl-2-phenyl-1-(4-sulphamoylphenyl)pyrrole,

2-(3,4-dimethylphenyl)-4-methyl-1-(4-sulphamoylphenyl)pyrrole,

2-(3-chloro-4-methoxyphenyl)-4-methyl-1-(4-sulphamoylphenyl)pyrrole,

4-methyl-1-(4-methylthiophenyl)-2-(4-sulphamoylphenyl)pyrrole,

5-chloro-1-(4-methoxyphenyl)-2-(4-sulphamoylphenyl)pyrrole,

1-(3,4-dimethylphenyl)-4-methyl-2-(4-sulphamoylphenyl)pyrrole,

5-chloro-1-(4-ethoxyphenyl)-2-(4-sulphamoylphenyl)pyrrole,

5-chloro-1-(4-methylthiophenyl)-2-(4-sulphamoylphenyl)pyrrole,

1-(4-ethylthiophenyl)-4-methyl-2-(4-sulphamoylphenyl)pyrrole,

2-(3,5-dimethylphenyl)-4-methyl-1-(4-sulphamoylphenyl)pyrrole,

1-(4-mercaptophenyl)-4-methyl-2-(4-sulphamoylphenyl)pyrrole,

1-(4-acetylthiophenyl)-4-methyl-2-(4-sulphamoylphenyl)pyrrole,

1-(4-acetylaminosulphonylphenyl)-4-methyl-2-(4-methoxyphenyl)pyrrole, or

1-(4-acetylaminosulphonylphenyl)-4-methyl-2-(3,4-dimethylphenyl)pyrrole,

or a pharmaceutically acceptable salt thereof.

41. A use according to Claim 29, in which said active compound is:

2-(4-chlorophenyl)-4-methyl-1-(4-sulphamoylphenyl)pyrrole,

2-(4-ethoxyphenyl)-4-methyl-1-(4-sulphamoylphenyl)pyrrole,

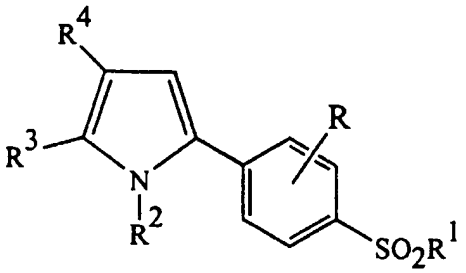
2-(3,4-dimethylphenyl)-4-methyl-1-(4-sulphamoylphenyl)pyrrole,

4-methyl-1-(4-methylthiophenyl)-2-(4-sulphamoylphenyl)pyrrole, or

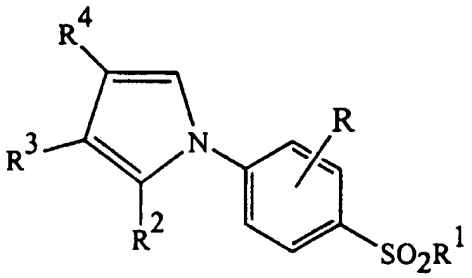
1-(4-acetylaminosulphonylphenyl)-4-methyl-2-(3,4-dimethylphenyl)pyrrole,

or a pharmaceutically acceptable salt thereof.

42. The use of a compound of formula (I) or (II):



(I)



(II)

in which

R represents a hydrogen atom, a halogen atom or a lower alkyl group;

R^1 represents a lower alkyl group, an amino group or a group of formula $-NHR^a$ (in which R^a represents a group which may be eliminated *in vivo);*

R^2 represents a phenyl group or a phenyl group substituted by at least one of substituents α or substituents β, defined below;

R^3 represents a hydrogen atom, a halogen atom, a lower alkyl group or a lower alkyl group substituted by at least one of substituents α;

R^4 represents a hydrogen atom, a lower alkyl group, a lower alkyl group substituted by at least one of substituents α, a cycloalkyl group, an aryl group a defined below, or an aralkyl group as defined below;

said aryl group is a carbocyclic aromatic hydrocarbon group having from 6 to 14 carbon atoms in one or more aromatic rings or such a group which is fused to a cycloalkyl group having from 3 to 10 carbon atoms, and the group is unsubstituted or it is substituted by at least one of substituents α or substituents β;

said aralkyl group is a lower alkyl group which is substituted by one or more of the aryl groups defined above;

said substituents a are selected from hydroxy groups, halogen atoms, lower alkoxy groups and lower alkylthio groups; and

said substituents β are selected from lower alkyl groups, alkanoyloxy groups, mercapto groups, alkanoylthio

groups, lower alkylsulphinyl groups, lower alkyl groups substituted by at least one of substituents α, cycloalkyloxy groups, lower haloalkoxy groups and lower alkylenedioxy groups;

or a pharmaceutically acceptable salt thereof
for the manufacture of a medicament for inhibiting tumour growth in a mammal.

43. A use according to Claim 42, in which R represents a hydrogen atom, a fluorine atom, a chlorine atom or a methyl group.

44. A use according to Claim 43, in which R represents a hydrogen atom.

45. A use according to any one of Claims 42 to 44, in which R^1 represents a methyl group, an amino group or an acetylamino group.

46. A use according to Claim 45, in which R^1 represents an amino group or an acetylamino group.

47. A use according to any one of Claims 42 to 46, in which R^2 represents a phenyl group or a phenyl group substituted with at least one of substituents α^1 or substituents β^1;

substituents α^1 are selected from halogen atoms, lower alkoxy groups and lower alkylthio groups; and

substituents β^1 are selected from lower alkyl groups, mercapto groups, alkanoylthio groups, lower alkyl groups substituted with at least one of substituents α^1, lower haloalkoxy groups and lower alkylenedioxy groups.

48. A use according to Claim 47, in which R^2 represents a phenyl group or a phenyl group substituted with at least one of substituents α^1 or substituents β^2;

substituents α^1 are selected from halogen atoms, lower alkoxy groups and lower alkylthio groups.

substituents β^2 are selected from lower alkyl groups, mercapto groups, alkanoylthio groups, lower alkyl groups substituted with a halogen atom, lower haloalkoxy groups and lower alkylenedioxy groups.

49. A use according to any one of Claims 42 to 48, in which R^3 represents a hydrogen atom, a halogen atom, a lower alkyl group or a lower alkyl group substituted with at least one of substituents α^1;
substituents α^1 are selected from halogen atoms, lower alkoxy groups and lower alkylthio groups.

50. A use according to Claim 49, in which R^3 represents a hydrogen atom, a halogen atom, a lower alkyl group or a lower alkyl group substituted with a halogen atom.

51. A use according to any one of Claims 42 to 50, in which R^4 represents a hydrogen atom, a lower alkyl group, a lower alkyl group substituted with at least one of substituents α, a cycloalkyl group, an aryl group, an aryl group substituted with at least one of substituents α^1 or substituents β^3, an aralkyl group or an aralkyl group substituted with at least one of substituents α^1 or substituents β^3;

substituents α^1 are selected from halogen atoms, lower alkoxy groups and lower alkylthio groups; and

substituents β^3 are selected from lower alkyl groups, lower alkyl groups substituted with at least one of substituents a and cycloalkyloxy groups.

52. A use according to Claim 51, in which R^4 represents a hydrogen atom, a lower alkyl group, a lower alkyl group substituted with at least one of substituents α^2, a cycloalkyl group, an aryl group, an aryl group substituted with at least one of substituents α^2 or substituents β^4, an aralkyl group or an aralkyl group substituted with at least one of substituents α^2 or substituents β^4;

substituents α^2 are selected from hydroxy groups, halogen atoms and lower alkoxy groups; and

substituents β^4 are selected from lower alkyl groups, lower alkyl groups substituted with halogen atom and cycloalkyloxy groups.

53. A use according to Claim 42, in which said active compound is:

3-methyl-2-(4-methylphenyl)-1-(4-sulphamoylphenyl)pyrrole,

4-methyl-2-(4-methylphenyl)-1-(4-sulphamoylphenyl)pyrrole,

1-(4-fluorophenyl)-2-(4-sulphamoylphenyl)pyrrole,

1-(4-fluorophenyl)-4-methyl-2-(4-sulphamoylphenyl)pyrrole,

5-fluoro-1-(4-fluorophenyl)-2-(4-methylsulphonylphenyl)pyrrole,

2-(4-methoxyphenyl)-4-methyl-1-(4-sulphamoylphenyl)pyrrole,

1-(4-methoxyphenyl)-4-methyl-2-(4-sulphamoylphenyl)pyrrole,

4-ethyl-2-(4-methoxyphenyl)-1-(4-sulphamoylphenyl)pyrrole,

2-(4-chlorophenyl)-4-methyl-1-(4-sulphamoylphenyl)pyrrole,

4-methyl-2-(4-methylthiophenyl)-1-(4-sulphamoylphenyl)pyrrole,

2-(4-ethoxyphenyl)-4-methyl-1-(4-sulphamoylphenyl)pyrrole,

2-(4-methoxy-3-methylphenyl)-4-methyl-1-(4-sulphamoylphenyl)pyrrole,

2-(3-fluoro-4-methoxyphenyl)-4-methyl-1-(4-sulphamoylphenyl)pyrrole,

4-methyl-2-phenyl-1-(4-sulphamoylphenyl)pyrrole,

2-(3,4-dimethylphenyl)-4-methyl-1-(4-sulphamoylphenyl)pyrrole,

2-(3-chloro-4-methoxyphenyl)-4-methyl-1-(4-sulphamoylphenyl)pyrrole,

4-methyl-1-(4-methylthiophenyl)-2-(4-sulphamoylphenyl)pyrrole,

5-chloro-1-(4-methoxyphenyl)-2-(4-sulphamoylphenyl)pyrrole,

1-(3,4-dimethylphenyl)-4-methyl-2-(4-sulphamoylphenyl)pyrrole,

5-chloro-1-(4-ethoxyphenyl)-2-(4-sulphamoylphenyl)pyrrole,

5-chloro-1-(4-methylthiophenyl)-2-(4-sulphamoylphenyl)pyrrole,

1-(4-ethylthiophenyl)-4-methyl-2-(4-sulphamoylphenyl)pyrrole,

2-(3,5-dimethylphenyl)-4-methyl-1-(4-sulphamoylphenyl)pyrrole,

1-(4-mercaptophenyl)-4-methyl-2-(4-sulphamoylphenyl)pyrrole,

1-(4-acetylthiophenyl)-4-methyl-2-(4-sulphamoylphenyl)pyrrole,

1-(4-acetylaminosulphonylphenyl)-4-methyl-2-(4-methoxyphenyl)pyrrole, or

1-(4-acetylaminosulphonylphenyl)-4-methyl-2-(3,4-dimethylphenyl)pyrrole,

or a pharmaceutically acceptable salt thereof.

54. A use according to Claim 42, in which said active compound is:

2-(4-chlorophenyl)-4-methyl-1-(4-sulphamoylphenyl)pyrrole,

2-(4-ethoxyphenyl)-4-methyl-1-(4-sulphamoylphenyl)pyrrole,

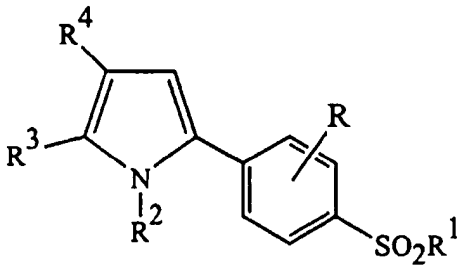
2-(3,4-dimethylphenyl)-4-methyl-1-(4-sulphamoylphenyl)pyrrole,

4-methyl-1-(4-methylthiophenyl)-2-(4-sulphamoylphenyl)pyrrole, or

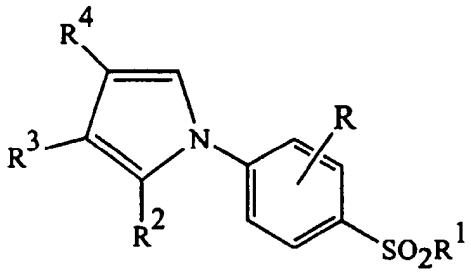
1-(4-acetylaminosulphonylphenyl)-4-methyl-2-(3,4-dimethylphenyl)pyrrole,

or a pharmaceutically acceptable salt thereof.

55. The use of a compound of formula (I) or (II):



(I)



(II)

in which

R represents a hydrogen atom, a halogen atom or a lower alkyl group;

R^1 represents a lower alkyl group, an amino group or a group of formula $-NHR^a$ (in which R^a represents a group which may be eliminated *in vivo*);

R^2 represents a phenyl group or a phenyl group substituted by at least one of substituents α or substituents β, defined below;

R^3 represents a hydrogen atom, a halogen atom, a lower alkyl group or a lower alkyl group substituted by at least one of substituents α;

R^4 represents a hydrogen atom, a lower alkyl group, a lower alkyl group substituted by at least one of substituents α, a cycloalkyl group, an aryl group a defined below, or an aralkyl group as defined below;

said aryl group is a carbocyclic aromatic hydrocarbon group having from 6 to 14 carbon atoms in one or more aromatic rings or such a group which is fused to a cycloalkyl group having from 3 to 10 carbon atoms, and the group is unsubstituted or it is substituted by at least one of substituents a or substituents β;

said aralkyl group is a lower alkyl group which is substituted by one or more of the aryl groups defined above;

said substituents a are selected from hydroxy groups, halogen atoms, lower alkoxy groups and lower alkylthio groups; and

said substituents β are selected from lower alkyl groups, alkanoyloxy groups, mercapto groups, alkanoylthio groups, lower alkylsulphinyl groups, lower alkyl groups substituted by at least one of substituents α, cycloalky-

loxy groups, lower haloalkoxy groups and lower alkylenedioxy groups;

or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for inhibiting tumor metastasis in a mammal.

56. A use according to Claim 55, in which R represents a hydrogen atom, a fluorine atom, a chlorine atom or a methyl group.

57. A use according to Claim 56, in which R represents a hydrogen atom.

58. A use according to any one of Claims 55 to 57, in which R^1 represents a methyl group, an amino group or an acetylamino group.

59. A use according to Claim 58, in which R^1 represents an amino group or an acetylamino group.

60. A use according to any one of Claims 55 to 59, in which R^2 represents a phenyl group or a phenyl group substituted with at least one of substituents α^1 or substituents β^1;

substituents α^1 are selected from halogen atoms, lower alkoxy groups and lower alkylthio groups; and

substituents β^1 are selected from lower alkyl groups, mercapto groups, alkanoylthio groups, lower alkyl groups substituted with at least one of substituents α^1, lower haloalkoxy groups and lower alkylenedioxy groups.

61. A use according to Claim 60, in which R^2 represents a phenyl group or a phenyl group substituted with at least one of substituents α^1 or substituents β^2;

substituents α^1 are selected from halogen atoms, lower alkoxy groups and lower alkylthio groups.

substituents β^2 are selected from lower alkyl groups, mercapto groups, alkanoylthio groups, lower alkyl groups substituted with a halogen atom, lower haloalkoxy groups and lower alkylenedioxy groups.

62. A use according to any one of Claims 55 to 61, in which R^3 represents a hydrogen atom, a halogen atom, a lower alkyl group or a lower alkyl group substituted with at least one of substituents α^1;
substituents α^1 are selected from halogen atoms, lower alkoxy groups and lower alkylthio groups.

63. A use according to Claim 62, in which R^3 represents a hydrogen atom, a halogen atom, a lower alkyl group or a lower alkyl group substituted with a halogen atom.

64. A use according to any one of Claims 55 to 63, in which R^4 represents a hydrogen atom, a lower alkyl group, a lower alkyl group substituted with at least one of substituents α, a cycloalkyl group, an aryl group, an aryl group substituted with at least one of substituents α^1 or substituents β^3, an aralkyl group or an aralkyl group substituted with at least one of substituents α^1 or substituents β^3;

substituents α^1 are selected from halogen atoms, lower alkoxy groups and lower alkylthio groups; and

substituents β^3 are selected from lower alkyl groups, lower alkyl groups substituted with at least one of substituents α and cycloalkyloxy groups.

65. A use according to Claim 64, in which R^4 represents a hydrogen atom, a lower alkyl group, a lower alkyl group substituted with at least one of substituents α^2, a cycloalkyl group, an aryl group, an aryl group substituted with at least one of substituents α^2 or substituents β^4, an aralkyl group or an aralkyl group substituted with at least one of substituents α^2 or substituents β^4;

substituents α^2 are selected from hydroxy groups, halogen atoms and lower alkoxy groups; and

substituents β^4 are selected from lower alkyl groups, lower alkyl groups substituted with halogen atom and cycloalkyloxy groups.

66. A use according to Claim 55, in which said active compound is:

3-methyl-2-(4-methylphenyl)-1-(4-sulphamoylphenyl)pyrrole,

4-methyl-2-(4-methylphenyl)-1-(4-sulphamoylphenyl)pyrrole,

1-(4-fluorophenyl)-2-(4-sulphamoylphenyl)pyrrole,

1-(4-fluorophenyl)-4-methyl-2-(4-sulphamoylphenyl)pyrrole,

5-fluoro-1-(4-fluorophenyl)-2-(4-methylsulphonylphenyl)pyrrole,

2-(4-methoxyphenyl)-4-methyl-1-(4-sulphamoylphenyl)pyrrole,

1-(4-methoxyphenyl)-4-methyl-2-(4-sulphamoylphenyl)pyrrole,

4-ethyl-2-(4-methoxyphenyl)-1-(4-sulphamoylphenyl)pyrrole,

2-(4-chlorophenyl)-4-methyl-1-(4-sulphamoylphenyl)pyrrole,

4-methyl-2-(4-methylthiophenyl)-1-(4-sulphamoylphenyl)pyrrole,

2-(4-ethoxyphenyl)-4-methyl-1-(4-sulphamoylphenyl)pyrrole,

2-(4-methoxy-3-methylphenyl)-4-methyl-1-(4-sulphamoylphenyl)pyrrole,

2-(3-fluoro-4-methoxyphenyl)-4-methyl-1-(4-sulphamoylphenyl)pyrrole,

4-methyl-2-phenyl-1-(4-sulphamoylphenyl)pyrrole,

2-(3,4-dimethylphenyl)-4-methyl-1-(4-sulphamoylphenyl)pyrrole,

2-(3-chloro-4-methoxyphenyl)-4-methyl-1-(4-sulphamoylphenyl)pyrrole,

4-methyl-1-(4-methylthiophenyl)-2-(4-sulphamoylphenyl)pyrrole,

5-chloro-1-(4-methoxyphenyl)-2-(4-sulphamoylphenyl)pyrrole,

1-(3,4-dimethylphenyl)-4-methyl-2-(4-sulphamoylphenyl)pyrrole,

5-chloro-1-(4-ethoxyphenyl)-2-(4-sulphamoylphenyl)pyrrole,

5-chloro-1-(4-methylthiophenyl)-2-(4-sulphamoylphenyl)pyrrole,

1-(4-ethylthiophenyl)-4-methyl-2-(4-sulphamoylphenyl)pyrrole,

2-(3,5-dimethylphenyl)-4-methyl-1-(4-sulphamoylphenyl)pyrrole,

1-(4-mercaptophenyl)-4-methyl-2-(4-sulphamoylphenyl)pyrrole,

1-(4-acetylthiophenyl)-4-methyl-2-(4-sulphamoylphenyl)pyrrole,

1-(4-acetylaminosulphonylphenyl)-4-methyl-2-(4-methoxyphenyl)pyrrole, or

1-(4-acetylaminosulphonylphenyl)-4-methyl-2-(3,4-dimethylphenyl)pyrrole,

or a pharmaceutically acceptable salt thereof.

67. A use according to Claim 55, in which said active compound is:

2-(4-chlorophenyl)-4-methyl-1-(4-sulphamoylphenyl)pyrrole,

2-(4-ethoxyphenyl)-4-methyl-1-(4-sulphamoylphenyl)pyrrole,

2-(3,4-dimethylphenyl)-4-methyl-1-(4-sulphamoylphenyl)pyrrole,

4-methyl-1-(4-methylthiophenyl)-2-(4-sulphamoylphenyl)pyrrole, or

1-(4-acetylaminosulphonylphenyl)-4-methyl-2-(3,4-dimethylphenyl)pyrrole,

or a pharmaceutically acceptable salt thereof.

European Patent Office

EUROPEAN SEARCH REPORT

Application Number
EP 98 31 0510

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